Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
July 12, 2017
4 p.m.

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

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – July 12, 2017

DATE: July 3, 2017

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

Enclosed are the following items related to the July 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/Opioid Initiative Update – Appendix B

Action Item – Vote to Prior Authorize Austedo™ (Deutetrabenazine) and Xenazine® (Tetrabenazine) – Appendix C

Action Item – Vote to Update the Inhaled Tobramycin Products, Pulmozyme® (Dornase Alfa), and Cayston® (Aztreonam) Prior Authorization Criteria – Appendix D

Action Item – Vote to Prior Authorize Ingrezza™ (Valbenazine) – Appendix E

Action Item – Vote to Update the Atypical Antipsychotic Prior Authorization Criteria and Tier Chart – Appendix F

Action Item – Vote to Prior Authorize Carac® (Fluorouracil 0.5% Cream), GoNitro™ (Nitroglycerin Sublingual Powder), Soltamox® (Tamoxifen Citrate Oral Solution), Taytulla™ (Norethindrone Acetate/Ethinyl Estradiol Capsules & Ferrous Fumarate Capsules), Tirosint®-SOL (Levothyroxine Sodium Oral Solution), Xatmep™ (Methotrexate Oral Solution), Zovirax® (Acyclovir Ointment and Suspension), Xerese® (Acyclovir/Hydrocortisone Cream), & Denavir® (Penciclovir Cream) – Appendix G

Action Item – Vote to Prior Authorize Aczone® (Dapsone Gel) and Tazorac® (Tazarotene Cream and Gel) – Appendix H

Action Item – Vote to Prior Authorize Vyvanse® (Lisdexamfetamine Chewable Tablets) and Update the ADHD Prior Authorization Criteria and Tier Chart – Appendix I

30-Day Notice to Prior Authorize Radicava™ (Edaravone) – Appendix J

Annual Review of Atopic Dermatitis (AD) Medications and 30-Day Notice to Prior Authorize Eucrisa™ (Crisaborole 2% Ointment), Dupixent® (Dupilumab Injection), & Prudoxin™ and Zonalon® (Doxepin 5% Cream) – Appendix K

30-Day Notice to Prior Authorize Vimizim® (Elosulfase Alfa) – Appendix L

Annual Review of Natpara® (Parathyroid Hormone Injection) and 30-Day Notice to Prior Authorize Rayaldee® (Calcifediol), Parsabiv™ (Etelcalcetide), Zemplar® (Paricalcitol Capsules), and Hectorol® (Doxercalciferol Capsules) – Appendix M

Annual Review of Opioid Analgesics and Opioid Medication Assisted Treatment (MAT) Medications & 30-Day Notice to Prior Authorize Arymo™ ER (Morphine Sulfate Extended-Release), Troxyca® ER (Oxycodone/Naltrexone Extended-Release), Vantrela™ ER (Hydrocodone Extended-Release), Oxaydo® (Oxycodone), and RoxyBond™ (Oxycodone) – Appendix N

30-Day Notice to Prior Authorize Brineura™ (Cerliponase Alfa) – Appendix O

Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Marplan® (Isocarboxazid) and Desyrel® (Trazodone 300mg Tablets) – Appendix P

Annual Review of Fibric Acid Derivative Medications and 30-Day Notice to Prior Authorize Choline Fenofibrate Delayed-Release (Trilipix®) 135mg Capsules and Fenofibrate Micronized (Lofibra®) 200mg Capsules – Appendix Q

Annual Review of Fibromyalgia Medications – Appendix R

Annual Review of Ocaliva® (Obeticholic Acid) – Appendix S

Industry News and Updates – Appendix T

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – July 12, 2017 @ 4:00 p.m.

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call to Order

A. Roll Call – Dr. Cothran

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum

A. 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. June 14, 2017 DUR Minutes – Vote
B. June 14, 2017 DUR Recommendations Memorandum

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

4. Update on Medication Coverage Authorization Unit/SoonerCare Opioid Initiative Update – See Appendix B

A. Medication Coverage Activity for June 2017
B. Pharmacy Help Desk Activity for June 2017
C. SoonerCare Opioid Initiative Update

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

5. Action Item – Vote to Prior Authorize Austedo™ (Deutetrabenazine) and Xenazine® (Tetrabenazine) – See Appendix C

A. Introduction
B. Xenazine® (Tetrabenazine) Off-Label Uses
C. College of Pharmacy Recommendations

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

6. Action Item – Vote to Update the Inhaled Tobramycin Products, Pulmozyme® (Dornase Alfa), and Cayston® (Aztreonam) Prior Authorization Criteria – See Appendix D

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Ingrezza™ (Valbenazine) – See Appendix E

A. Introduction
B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Update the Atypical Antipsychotic Prior Authorization Criteria and Tier Chart – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations
C. Recommended Prior Authorization Criteria

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

9. Action Item – Vote to Prior Authorize Carac® (Fluorouracil 0.5% Cream), GoNitro™ (Nitroglycerin Sublingual Powder), Soltamox® (Tamoxifen Citrate Oral Solution), Taytulla™ (Norethindrone Acetate/Ethinyl Estradiol Capsules & Ferrous Fumarate Capsules), Tirosint®-SOL (Levothyroxine Sodium Oral Solution), Xatmep™ (Methotrexate Oral Solution), Zovirax® (Acyclovir Ointment and Suspension), Xerese® (Acyclovir/Hydrocortisone Cream), & Denavir® (Penciclovir Cream) – See Appendix G

A. Introduction
B. College of Pharmacy Recommendations

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

10. Action Item – Vote to Prior Authorize Aczone® (Dapsone Gel) and Tazorac® (Tazarotene Cream and Gel) – See Appendix H

A. Introduction
B. College of Pharmacy Recommendations

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

11. Action Item – Vote to Prior Authorize Vyvanse® (Lisdexamfetamine Chewable Tablets) and Update the ADHD Prior Authorization Criteria and Tier Chart – See Appendix I

A. Introduction
B. College of Pharmacy Recommendations

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

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

A. Introduction
B. Market News and Updates
C. Radicava™ (Edaravone) Product Summary
D. College of Pharmacy Recommendations

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

13. Annual Review of Atopic Dermatitis (AD) Medications and 30-Day Notice to Prior Authorize Eucrisa™ (Crisaborole 2% Ointment), Dupixent® (Dupilumab Injection), & Prudoxin™ and Zonalon® (Doxepin 5% Cream) – See Appendix K

A. Current Prior Authorization Criteria
B. Utilization of AD Medications
C. Prior Authorization of AD Medications
D. Market News and Updates
E. Eucrisa™ (Crisaborole 2% Ointment) Product Summary
F. Dupixent® (Dupilumab Injection) Product Summary
G. Prudoxin™ and Zonalon® (Doxepin 5% Cream) Product Summary
H. College of Pharmacy Recommendations
I. Utilization Details of AD Medications

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

14. 30-Day Notice to Prior Authorize Vimizim® (Elosulfase Alfa) – See Appendix L

A. Introduction
B. Vimizim® (Elosulfase Alfa) Product Summary
C. College of Pharmacy Recommendations

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

15. Annual Review of Natpara® (Parathyroid Hormone Injection) and 30-Day Notice to Prior Authorize Rayaldee® (Calcifediol), Parsabiv™ (Etelcalcetide), Zemplar® (Paricalcitol Capsules), and Hectorol® (Doxercalciferol Capsules) – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of Parathyroid Medications
C. Prior Authorization of Natpara®, Calcimimetics, and Vitamin D Analogs
D. Market News and Updates
E. Product Summaries

F. College of Pharmacy Recommendations
G. Utilization Details of Calcimimetics and Vitamin D Analogs
H. Utilization Details of Natpara® (Parathyroid Hormone Injection)

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

16. Annual Review of Opioid Analgesics and Opioid Medication Assisted Treatment (MAT) Medications & 30-Day Notice to Prior Authorize Arymo™ ER (Morphine Sulfate Extended-Release), Troxyca® ER (Oxycodone/Naltrexone Extended-Release), Vantrela™ ER (Hydrocodone Extended-Release), Oxaydo® (Oxycodone), and RoxyBond™ (Oxycodone) – See Appendix N

A. Current Prior Authorization Criteria
B. Utilization of Opioid Analgesics and MAT Medications
C. Prior Authorization of Opioid Analgesics & MAT Medications
D. Market News and Updates
E. Product Summaries
F. College of Pharmacy Recommendations
G. Utilization Details of Opioid Analgesics
H. Utilization Details of MAT Medications

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

17. 30-Day Notice to Prior Authorize Brineura™ (Cerliponase Alfa) – See Appendix O

A. Introduction
B. Market News and Updates
C. Brineura™ (Cerliponase Alfa) Product Summary
D. College of Pharmacy Recommendations

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

18. Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Marplan® (Isocarboxazid) and Desyrel® (Trazodone 300mg Tablets) – See Appendix P

A. Current Prior Authorization Criteria
B. Utilization of Antidepressants
C. Prior Authorization of Antidepressants
D. Market News and Updates
E. Marplan® (Isocarboxazid) Product Summary
F. Cost Comparison
G. College of Pharmacy Recommendations
H. Utilization Details of Antidepressants

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

19. Annual Review of Fibric Acid Derivative Medications and 30-Day Notice to Prior Authorize Choline Fenofibrate Delayed-Release (Trilipix®) 135mg Capsules and Fenofibrate Micronized (Lofibra®) 200mg Capsules – See Appendix Q

A. Current Prior Authorization Criteria
B. Utilization of Fibric Acid Derivative Medications
C. Prior Authorization of Fibric Acid Derivative Medications
D. Market News and Updates
E. Cost Comparison
F. College of Pharmacy Recommendations
G. Utilization Details of Fibric Acid Derivative Medications

Non-Presentation; Questions Only:

20. Annual Review of Fibromyalgia Medications – See Appendix R

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

Non-Presentation; Questions Only:

21. Annual Review of Ocaliva® (Obeticholic Acid) – See Appendix S

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

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

22. Industry News and Updates – See Appendix T

A. Introduction
B. News and Updates

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

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

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

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

No meeting scheduled for August 2017.

A. Synagis® (Palivizumab)
B. Growth Hormone
C. Fabrazyme® (Agalsidase Beta)
D. Allergy Immunotherapies
E. Breast Cancer
F. Hemophilia Medications
G. Insomnia Medications
H. Alzheimer's Medications
I. Anticoagulants & Platelet Aggregation Inhibitors

**Future business subject to change.*

25. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF JUNE 14, 2017

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

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Melissa Abbott, Pharm.D.; Clinical Pharmacist	x	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Emily Borders, Pharm.D.; Assistant Professor	x	
Wendi Chandler, Pharm.D.; Clinical Pharmacist	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Erin Ford, Pharm.D.; Clinical Pharmacist		x
Bethany Holderread, Pharm.D.; Clinical Coordinator	x	
Shellie Keast, Ph.D.; Assistant Professor		x
Carol Moore, Pharm.D.; Clinical Pharmacist		x
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Stephanie Nichols, Pharm.D.; Clinical Pharmacist	x	
Timothy Pham, Ph.D.; Postdoctoral Research Fellow	x	
Leslie Robinson, D.Ph.; PA Coordinator		x
Sarah Schmidt, Pharm.D.; Clinical Assistant Professor	x	
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist	x	
Graduate Students: Christina Bulkley, Pharm.D.		x
Corby Thompson, Pharm.D.	x	
Visiting Pharmacy Student(s): Tucker Olsen	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	x	
Kelli Brodersen, Marketing Coordinator	x	
Robert Evans, M.D.; Sr. Medical Director	x	
Michael Herndon, D.O.; Chief Medical Officer		x
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist		x
Garth Splinter, M.D.; M.B.A.; Deputy Chief Executive Officer	x	
Joseph Young, Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Deron Grothe, Teva Pharma	Anthony Locke, Tris Pharma	Edie Dodson, Genzyme
Torey Batts, Teva Pharma	Rose Mullen, Alkermes	Dean Meyer, Takeda
Doug Wood, ViiV	Tyler Craddock, The Medicines Co.	Peter Magargee, Allergan
Mark Herlehy, Lundbeck	Kristin Pareja, Otsuka	Gay Thomas, BMS
Marc Parker, Sunovion	Matt Forney, Merck	Jason Schwier, Amgen
Terry McCurren, Otsuka America	Brent Hildebrand, Gilead	Toby Thompson, Pfizer
Mary Stewart Crane, J & J	James Gaustad, Pharma L.P.	Gwendolyn Caldwell, PhRMA
Brian Maves, Pfizer	Chad Farris, Neurocrine	Kent Douglas, Neurocrine

PRESENT FOR PUBLIC COMMENT:	
Torey Batts	Teva Pharmaceuticals
Marsie Ross	Tris Pharmaceuticals
Rose Mullen	Alkermes
Kristin Pareja	Otsuka
Monica Guillory	Neurocrine

AGENDA ITEM NO. 1: **CALL TO ORDER**

1A: ROLL CALL

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

ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: **PUBLIC COMMENT FORUM**

2A: AGENDA ITEM NO. 13 SPEAKER: MARSIE ROSS
2B: AGENDA ITEM NO. 14 SPEAKER: ROSE MULLEN
2C: AGENDA ITEM NO. 14 SPEAKER: KRISTIN PAREJA
2D: AGENDA ITEM NO. 15 SPEAKER: TOREY BATTS
2E: AGENDA ITEM NO. 17 SPEAKER: MONICA GUILLORY

ACTION: NONE REQUIRED

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

3A: MAY 10, 2017 DUR MINUTES – VOTE
3B: MAY 10, 2017 DUR RECOMMENDATIONS MEMORANDUM

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/ CHLOROQUINE (ARALEN®) & HYDROXYCHLOROQUINE (PLAQUENIL®) INDUCED RETINOPATHY MAILING UPDATE**

4A: MEDICATION COVERAGE ACTIVITY FOR MAY 2017
4B: PHARMACY HELP DESK ACTIVITY FOR MAY 2017
4C: CHLOROQUINE (ARALEN®) & HYDROXYCHLOROQUINE (PLAQUENIL®) INDUCED RETINOPATHY MAILING UPDATE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE KUVAN® (SAPROPTERIN)**

5A: INTRODUCTION
5B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Nawaz
Dr. Harrell moved to approve; seconded by Dr. Huddleston

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: **VOTE TO PRIOR AUTHORIZE LUMIZYME® (ALGLUCOSIDASE ALFA INJECTION)**

6A: INTRODUCTION

6B: 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. 7: **VOTE TO PRIOR AUTHORIZE ALPHA$_1$-PROTEINASE INHIBITORS: ARALAST NP™, GLASSIA®, PROLASTIN®-C, AND ZEMAIRA®**

7A: INTRODUCTION

7B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler
Dr. Preslar moved to approve; seconded by Dr. Garton

ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: **VOTE TO PRIOR AUTHORIZE ELAPRASE® (IDURSULFASE)**

8A: INTRODUCTION

8B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Adams
Dr. Harrell moved to approve; seconded by Dr. Huddleston

ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: **VOTE TO PRIOR AUTHORIZE COLPREP™ KIT (SODIUM SULFATE/POTASSIUM SULFATE/MAGNESIUM SULFATE)**

9A: INTRODUCTION

9B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Nichols
Dr. Preslar moved to approve; seconded by Dr. Garton

ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: **VOTE TO PRIOR AUTHORIZE IMPAVIDO® (MILTEFOSINE)**

10A: INTRODUCTION

10B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Abbott
Dr. Harrell moved to approve; seconded by Dr. Munoz

ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: **VOTE TO PRIOR AUTHORIZE XALKORI® (CRIZOTINIB), ZYKADIA® (CERITINIB), ALECENSA® (ALECTINIB), ALUNBRIG™ (BRIGATINIB), TARCEVA® (ERLOTINIB), GILOTRIF® (AFATINIB), TAGRISSO™ (OSIMERTINIB), CYRAMZA® (RAMUCIRUMAB), AND TECENTRIQ® (ATEZOLIZUMAB)**

11A: INTRODUCTION

11B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Schmidt, Dr. Borders
Dr. Garton moved to approve; seconded by Dr. Huddleston

ACTION: MOTION CARRIED

AGENDA ITEM NO. 12: **ANNUAL REVIEW OF PROSTATE CANCER MEDICATIONS**

12A: INTRODUCTION

12B: CURRENT PRIOR AUTHORIZATION CRITERIA

12C: UTILIZATION OF PROSTATE CANCER MEDICATIONS

12D: MARKET NEWS AND UPDATES

12E: RECOMMENDATIONS

12F: UTILIZATION DETAILS OF PROSTATE CANCER MEDICATIONS

Materials included in agenda packet; presented by Dr. Schmidt, Dr. Borders
Dr. Preslar moved to approve; seconded by Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF ADHD AND NARCOLEPSY MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE VYVANSE® (LISDEXAMFETAMINE CHEWABLE TABLETS) AND UPDATE THE ADHD PRIOR AUTHORIZATION CRITERIA AND TIER CHART

13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF ADHD & NARCOLEPSY MEDICATIONS
13C: PRIOR AUTHORIZATION OF ADHD & NARCOLEPSY MEDICATIONS
13D: MARKET NEWS AND UPDATES
13E: MEDICAID DRUG REBATE PROGRAM
13F: COLLEGE OF PHARMACY RECOMMENDATIONS
13G: UTILIZATION DETAILS OF ADHD & NARCOLEPSY MEDICATIONS

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

AGENDA ITEM NO. 14: ANNUAL REVIEW OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS AND 30-DAY NOTICE TO UPDATE THE ATYPICAL ANTIPSYCHOTIC PRIOR AUTHORIZATION CRITERIA AND TIER CHART

14A: CURRENT PRIOR AUTHORIZATION CRITERIA
14B: UTILIZATION OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS
14C: PRIOR AUTHORIZATION OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS
14D: MARKET NEWS AND UPDATES
14E: MEDICAID DRUG REBATE PROGRAM
14F: COLLEGE OF PHARMACY RECOMMENDATIONS
14G: UTILIZATION DETAILS OF ATPICAL ANTIPSYCHOTIC MEDICATIONS

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

AGENDA ITEM NO. 15: ANNUAL REVIEW OF HUNTINGTON'S DISEASE (HD) MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE AUSTEDO™ (DEUTETRABENAZINE) AND XENAZINE® (TETRABENAZINE)

15A: INTRODUCTION
15B: CHOREA IN HD TREATMENT SUMMARY
15C: XENAZINE® (TETRABENAZINE) OFF-LABEL USES
15D: UTILIZATION OF HD MEDICATIONS
15E: MARKET NEWS AND UPDATES
15F: AUSTEDO™ (DEUTETRABENAZINE) PRODUCT SUMMARY
15G: XENAZINE® (TETRABENAZINE) PRODUCT SUMMARY
15H: COLLEGE OF PHARMACY RECOMMENDATIONS
15I: UTILIZATION DETAILS OF HD MEDICATIONS

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

AGENDA ITEM NO. 16: ANNUAL REVIEW OF INHALED TOBRAMYCIN PRODUCTS, PULMOZYME® (DORNASE ALFA), AND CAYSTON® (AZTREONAM)

16A: CURRENT PRIOR AUTHORIZATION CRITERIA
16B: UTILIZATION OF INHALED TOBRAMYCIN PRODUCTS, DORNASE ALFA, & AZTREONAM INHALATION
16C: PRIOR AUTHORIZATION OF INHALED TOBRAMYCIN PRODUCTS, DORNASE ALFA, & AZTREONAM INHALATION
16D: MARKET NEWS AND UPDATES
16E: INHALED TOBRAMYCIN TREATMENT COMPARISON

16F: COLLEGE OF PHARMACY RECOMMENDATIONS
16G: UTILIZATION DETAILS OF INHALED TOBRAMYCIN PRODUCTS, DORNASE ALFA, & AZTREONAM INHALATION
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: 30-DAY NOTICE TO PRIOR AUTHORIZE INGREZZA™ (VALBENAZINE)
17A: TARDIVE DYSKINESIA
17B: MARKET NEWS AND UPDATES
17C: INGREZZA™ (VALBENAZINE) PRODUCT SUMMARY
17D: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: ANNUAL REVIEW OF VARIOUS SPECIAL FORMULATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE CARAC® (FLUOROURACIL 0.5% CREAM), GONITRO™ (NITROGLYCERIN SUBLINGUAL POWDER), SOLTAMOX® (TAMOXIFEN CITRATE ORAL SOLUTION), TAYTULLA™ (NORETHINDRONE ACETATE/ETHINYL ESTRADIOL CAPSULES & FERROUS FUMARATE CAPSULES), TIROSINT®-SOL (LEVOTHYROXINE SODIUM ORAL SOLUTION), XATMEP™ (METHOTREXATE ORAL SOLUTION), ZOVIRAX® (ACYCLOVIR OINTMENT AND SUSPENSION), XERESE® (ACYCLOVIR/HYDROCORTISONE CREAM), & DENAVIR® (PENCICLOVIR CREAM)
18A: INTRODUCTION
18B: CURRENT PRIOR AUTHORIZATION CRITERIA
18D: UTILIZATION OF SPECIAL FORMULATIONS
18E: PRODUCT SUMMARIES
18F: COLLEGE OF PHARMACY RECOMMENDATIONS
18G: UTILIZATION DETAILS OF SPECIAL FORMULATIONS
Materials included in agenda packet; presented by Dr. Chandler
ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: 30-DAY NOTICE TO PRIOR AUTHORIZE ACZONE® (DAPSONE GEL) AND TAZORAC® (TAZAROTENE CREAM AND GEL)
19A: INTRODUCTION
19B: UTILIZATION OF ACZONE® (DAPSONE GEL)
19C: UTILIZATION OF TAZORAC® (TAZAROTENE CREAM AND GEL)
19D: MARKET NEWS AND UPDATES
19E: ACZONE® (DAPSONE GEL) PRODUCT SUMMARY
19F: TAZORAC® (TAZAROTENE CREAM AND GEL) PRODUCT SUMMARY
19G: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nichols
ACTION: NONE REQUIRED

AGENDA ITEM NO. 20: ANNUAL REVIEW OF H.P. ACTHAR® GEL (CORTICOTROPIN INJECTION)
20A: INTRODUCTION
20B: CURRENT PRIOR AUTHORIZATION CRITERIA
20C: UTILIZATION OF H.P. ACTHAR® GEL (CORTICOTROPIN INJECTION)
20D: PRIOR AUTHORIZATION OF H.P. ACTHAR® GEL (CORTICOTROPIN INJECTION)
20E: MARKET NEWS AND UPDATES
20F: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 21: **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. 22: **FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)**

22A: OPIOID ANALGESICS
22B: ANTIDEPRESSANT MEDICATIONS
22C: FIBRIC ACID MEDICATIONS
22D: ATOPIC DERMATITIS MEDICATIONS
22E: HYPOPARATHYROIDISM AND HYPERPARATHYROIDISM MEDICATIONS
22F: OCALIVA® (OBETICHOLIC ACID)
22G: BRINEURA™ (CERLIPONASE ALFA)
22H: RADICAVA™ (EDARAVONE)

Future business subject to change.

Materials included in agenda packet; presented by Dr. Holderread

ACTION: **NONE REQUIRED**

AGENDA ITEM NO. 23: **ADJOURNMENT**

The meeting was adjourned at 5:49 pm.

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

Memorandum

Date: June 15, 2017

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

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

Subject: DUR Board Recommendations from Meeting of June 14, 2017

Recommendation 1: Chloroquine (Aralen®) & Hydroxychloroquine (Plaquenil®) Induced Retinopathy Mailing Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Kuvan® (Sapropterin)

MOTION CARRIED. Approval was not unanimous.

The College of Pharmacy recommends the prior authorization of Kuvan® (sapropterin) with the following criteria:

Kuvan® (Sapropterin) Approval Criteria:

1. An FDA approved diagnosis of phenylketonuria; and
2. Documentation of active management with a phenylalanine restricted diet; and
3. Member must not have two null mutations in *trans*; and
4. Initial approvals will be for the duration of 30 days. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of greater than or equal to a 30% decrease in blood phenylalanine levels from baseline.

a. If the member was initiated at 10mg/kg/day dose, then a subsequent trial of 20mg/kg/day for a duration of 30 days can be approved. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of greater than or equal to a 30% decrease in blood phenylalanine levels from baseline.
b. If the member was initiated at 20mg/kg/day dose, then no additional approvals will be granted after a trial period of 30 days if the member did not respond to treatment as defined by laboratory documentation of greater than or equal to a 30% decrease in blood phenylalanine levels from baseline.

5. Subsequent approvals will be for the duration of one year.

Recommendation 3: Vote to Prior Authorize Lumizyme® (Alglucosidase Alfa Injection)

MOTION CARRIED. Approval was not unanimous.

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

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

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

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

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

Recommendation 4: Vote to Prior Authorize Alpha$_1$-Proteinase Inhibitors: Aralast NP™, Glassia®, Prolastin®-C, and Zemaira®

MOTION CARRIED by unanimous approval.

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

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

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

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

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

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

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

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

Recommendation 5: Vote to Prior Authorize Elaprase® (Idursulfase)

MOTION CARRIED. Approval was not unanimous.

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

Elaprase® (Idursulfase) Approval Criteria:

1. An FDA approved diagnosis of Hunter syndrome (mucopolysaccharidosis type II; MPS II) confirmed by:
    a. Enzyme assay demonstrating a deficiency of iduronate-2-sulfatase enzyme activity; or
    b. Molecular genetic testing confirming a hemizygous pathogenic variant in the *IDS* gene; and
2. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Recommendation 6: Vote to Prior Authorize ColPrep™ Kit (Sodium Sulfate/ Potassium Sulfate/Magnesium Sulfate)

MOTION CARRIED by unanimous approval.

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

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

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

Recommendation 7: Vote to Prior Authorize Impavido® (Miltefosine)

MOTION CARRIED by unanimous approval.

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

Impavido® (Miltefosine) Approval Criteria:

1. An FDA approved indication for treatment of:
    a. Visceral leishmaniasis due to *Leishmania donovani*; or
    b. Cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, or *Leishmania panamensis*; or
    c. Mucosal leishmaniasis due to *Leishmania braziliensis*; and
2. Female members must not be pregnant and female members of reproductive potential must have a pregnancy test prior to therapy initiation. Female members of reproductive potential must be willing to use effective contraception while on therapy and for five months after completion of therapy; and
3. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.
4. A quantity limit of 84 capsules per 28 days will apply.

Recommendation 8: Vote to Prior Authorize Xalkori® (Crizotinib), Zykadia® (Ceritinib), Alecensa® (Alectinib), Alunbrig™ (Brigatinib), Tarceva® (Erlotinib), Gilotrif® (Afatinib), Tagrisso™ (Osimertinib), Cyramza® (Ramucirumab), and Tecentriq® (Atezolizumab)

MOTION CARRIED by unanimous approval.

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

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

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

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

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

1. A diagnosis of metastatic NSCLC; and
2. Anaplastic lymphoma kinase (ALK) positivity; and
3. Ceritinib must be used as a single-agent only.

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

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

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

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

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

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

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

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

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

1. A diagnosis of pancreatic cancer; and
2. Locally advanced unresectable or metastatic disease; and
3. Member must have good performance status (ECOG 0 to 2); and
4. Erlotinib must be used as a first-line agent only; and
5. Erlotinib must be used in combination with gemcitabine.

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

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

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

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

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

1. A diagnosis of pancreatic adenocarcinoma; and
2. Locally advanced unresectable disease or metastatic disease; and
3. Member must have good performance status (ECOG 0 to 2); and
4. Erlotinib must be used in combination with gemcitabine.

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

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

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

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

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

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

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

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

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

4. Osimertinib must be used for subsequent therapy only.

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

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

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

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

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

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

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

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

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

1. A diagnosis of NSCLC; and
2. Subsequent therapy for metastatic disease; and
3. Member must have an ECOG performance score of 0 to 2; and
4. Atezolizumab must be used as a single-agent only.

Tecentriq® (Atezolizumab) Approval Criteria [Urothelial Carcinoma]:

1. A diagnosis of locally advanced or metastatic urothelial carcinoma; and
2. Progressed on or following platinum containing chemotherapy or in cisplatin ineligible patients.

Recommendation 9: Annual Review of Prostate Cancer Medications

NO ACTION REQUIRED.

Recommendation 10: Annual Review of ADHD and Narcolepsy Medications and 30-Day Notice to Prior Authorize Vyvanse® (Lisdexamfetamine Chewable Tablets) and Update the ADHD Prior Authorization Criteria and Tier Chart

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Atypical Antipsychotic Medications and 30-Day Notice to Update the Atypical Antipsychotic Prior Authorization Criteria and Tier Chart

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Huntington's Disease (HD) Medications and 30-Day Notice to Prior Authorize Austedo™ (Deutetrabenazine) and Xenazine® (Tetrabenazine)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Inhaled Tobramycin Products, Pulmozyme® (Dornase Alfa), and Cayston® (Aztreonam)

NO ACTION REQUIRED.

Recommendation 14: 30-Day Notice to Prior Authorize Ingrezza™ (Valbenazine)

NO ACTION REQUIRED.

Recommendation 15: Annual Review of Various Special Formulations and 30-Day Notice to Prior Authorize Carac® (Fluorouracil 0.5% Cream), GoNitro™ (Nitroglycerin Sublingual Powder), Soltamox® (Tamoxifen Citrate Oral Solution), Taytulla™ (Norethindrone Acetate/Ethinyl Estradiol Capsules & Ferrous Fumarate Capsules), Tirosint®-SOL (Levothyroxine Sodium Oral Solution), Xatmep™ (Methotrexate Oral Solution), Zovirax® (Acyclovir Ointment and Suspension), Xerese® (Acyclovir/Hydrocortisone Cream), & Denavir® (Penciclovir Cream)

NO ACTION REQUIRED.

Recommendation 16: 30-Day Notice to Prior Authorize Aczone® (Dapsone Gel) and Tazorac® (Tazarotene Cream and Gel)

NO ACTION REQUIRED.

Recommendation 17: Annual Review of H.P. Acthar® Gel (Corticotropin Injection)

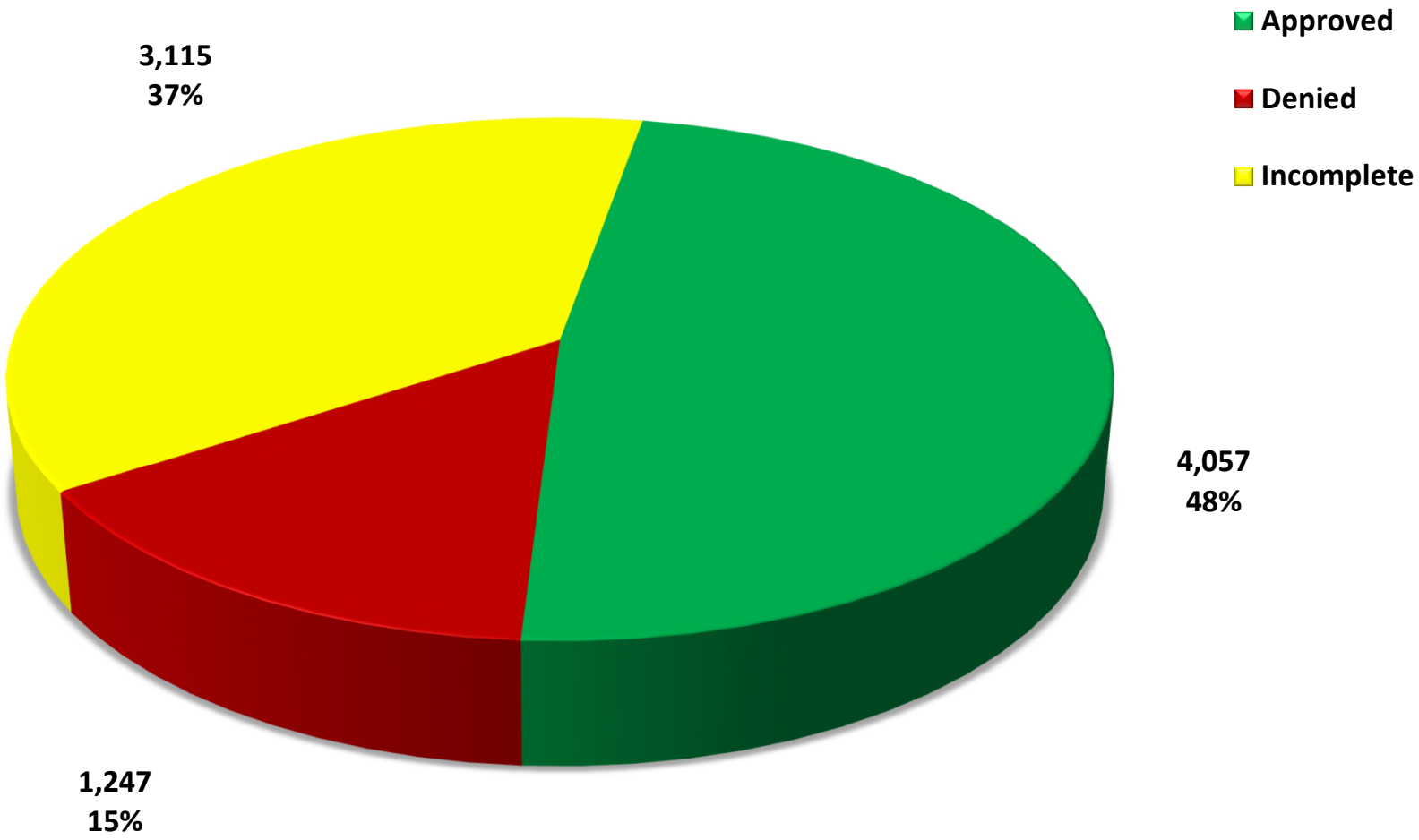
NO ACTION REQUIRED.

Recommendation 18: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

NO ACTION REQUIRED.

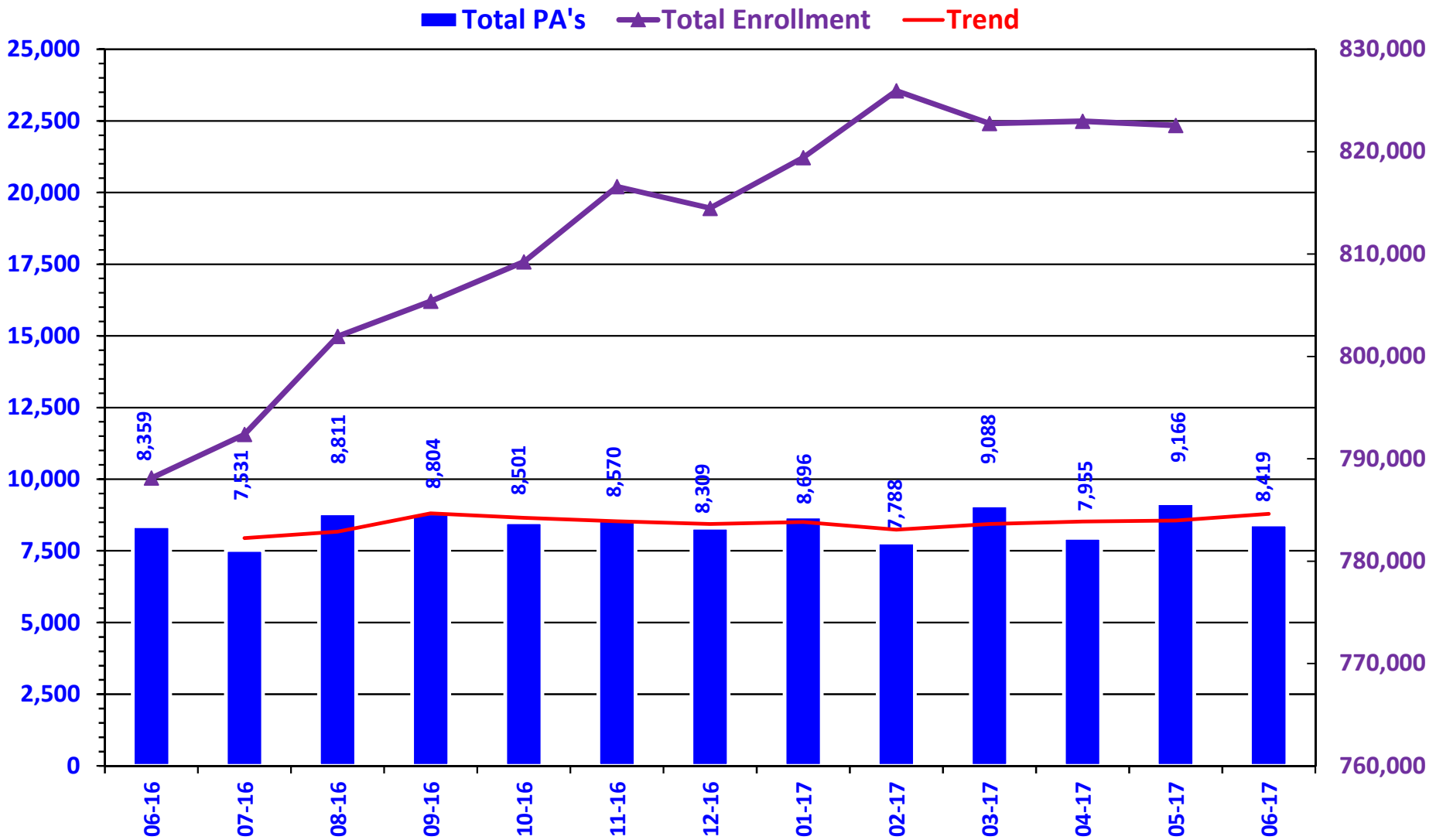
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: JUNE 2017



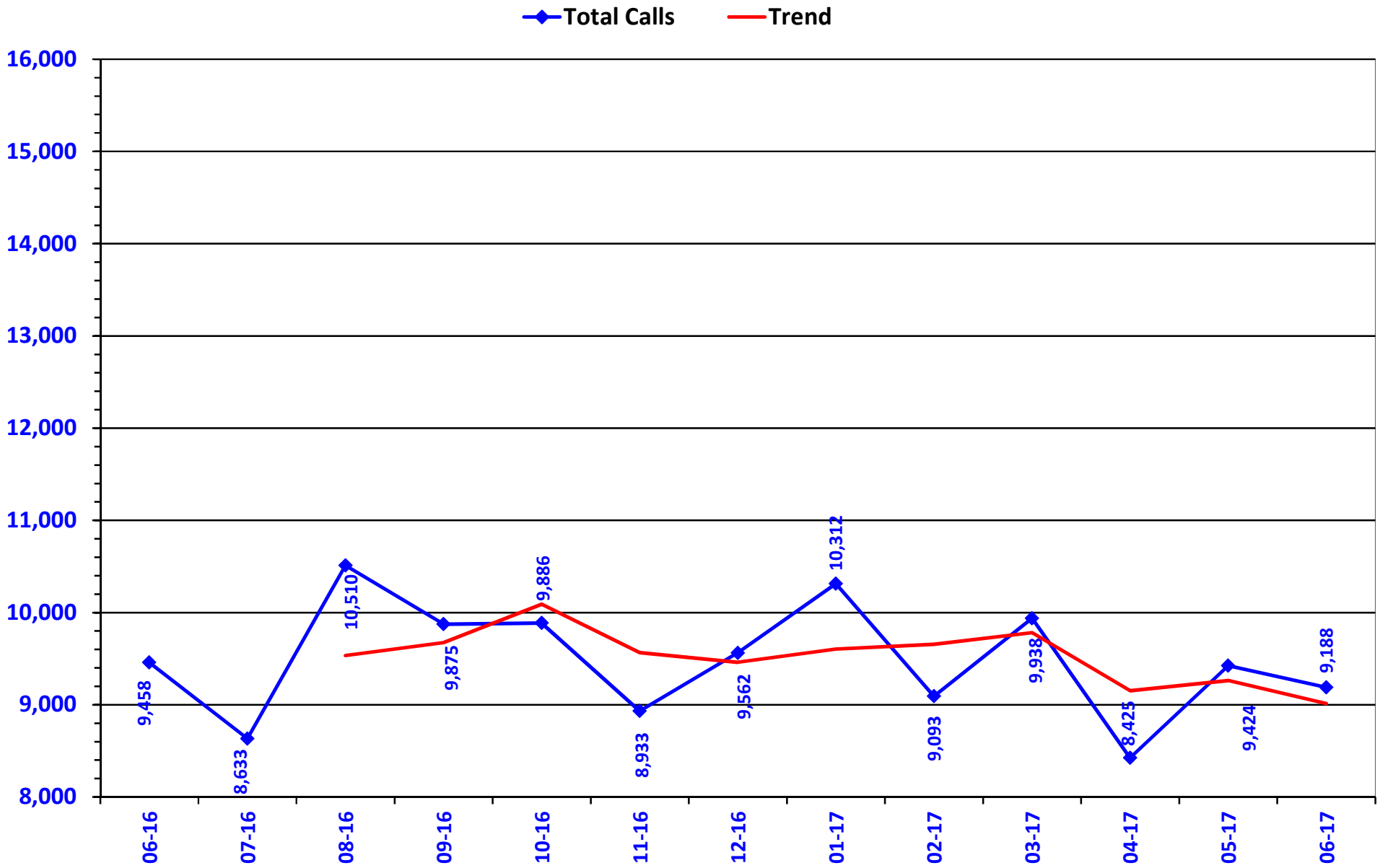
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: JUNE 2016 – JUNE 2017



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
JUNE 2016 – JUNE 2017



Prior Authorization Activity
6/1/2017 Through 6/30/2017

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	138	19	23	96	332
Analgesic - NonNarcotic	24	0	3	21	0
Analgesic - Narcotic	466	232	57	177	164
Antiasthma	26	6	6	14	341
Antibiotic	19	3	4	12	207
Anticonvulsant	123	41	22	60	317
Antidepressant	123	27	28	68	334
Antidiabetic	243	105	31	107	353
Antihistamine	246	208	9	29	351
Antimigraine	32	9	9	14	206
Antineoplastic	60	35	3	22	160
Antiparasitic	18	2	4	12	18
Antiulcers	158	37	48	73	165
Antiviral	58	33	8	17	8
Anxiolytic	64	44	2	18	282
Atypical Antipsychotics	269	158	16	95	345
Biologics	111	45	28	38	285
Bladder Control	69	13	23	33	336
Blood Thinners	244	151	19	74	335
Botox	47	31	10	6	338
Buprenorphine Medications	319	229	18	72	72
Calcium Channel Blockers	15	6	1	8	120
Cardiovascular	118	56	14	48	335
Cephalosporins	18	11	0	7	51
Chronic Obstructive Pulmonary Disease	203	29	55	119	301
Constipation/Diarrhea Medications	155	20	61	74	193
Contraceptive	21	14	0	7	336
Corticosteroid	10	2	1	7	70
Dermatological	113	14	63	36	182
Diabetic Supplies	515	316	17	182	182
Endocrine & Metabolic Drugs	96	53	5	38	141
Erythropoietin Stimulating Agents	17	13	1	3	106
Fibromyalgia	236	45	94	97	312
Fish Oils	17	2	6	9	358
Gastrointestinal Agents	124	26	33	65	173
Genitourinary Agents	10	1	2	7	52
Glaucoma	14	1	5	8	11
Growth Hormones	83	54	5	24	146
Hepatitis C	73	52	8	13	7
HFA Rescue Inhalers	65	16	16	33	348
Insomnia	40	6	12	22	135
Insulin	82	28	16	38	346
Miscellaneous Antibiotics	24	2	8	14	9
Multiple Sclerosis	66	31	9	26	203
Muscle Relaxant	44	5	23	16	225

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Nasal Allergy	70	10	27	33	195
Neurological Agents	43	21	7	15	344
NSAIDs	209	28	68	113	281
Ocular Allergy	36	7	10	19	120
Osteoporosis	32	17	6	9	346
Other*	248	56	65	127	275
Otic Antibiotic	37	7	3	27	11
Respiratory Agents	17	11	0	6	185
Statins	73	15	14	44	339
Stimulant	777	431	56	290	326
Testosterone	72	12	26	34	334
Topical Antifungal	26	1	5	20	20
Topical Corticosteroids	124	3	36	85	65
Vitamin	63	25	19	19	278
Pharmacotherapy	98	79	0	19	256
Emergency PAs	1	1	0	0	
Total	**6,942**	**2,955**	**1,168**	**2,819**	
Overrides					
Brand	29	24	1	4	324
Cumulative Early Refill	4	4	0	0	180
Diabetic Supplies	4	3	1	0	239
Dosage Change	356	325	2	29	14
High Dose	4	4	0	0	271
Ingredient Duplication	34	25	0	9	16
Lost/Broken Rx	85	81	1	3	12
NDC vs Age	236	170	18	48	250
Nursing Home Issue	60	39	16	5	16
Opioid Quantity	23	22	1	0	161
Other*	21	15	1	5	10
Quantity vs. Days Supply	593	381	37	175	254
STBS/STBSM	15	9	0	6	87
Stolen	10	7	2	1	10
Third Brand Request	34	22	1	11	18
Overrides Total	**1,477**	**1,102**	**79**	**296**	
Total Regular PAs + Overrides	**8,419**	**4,057**	**1,247**	**3,115**	

Denial Reasons	
Unable to verify required trials.	2,393
Does not meet established criteria.	1,276
Lack required information to process request.	677

Other PA Activity	
Duplicate Requests	641
Letters	8,280
No Process	7
Changes to existing PAs	634
Helpdesk Initiated Prior Authorizations	682
PAs Missing Information	33

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

SoonerCare Opioid Initiative Update

Oklahoma Health Care Authority
July 2017

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

Opioid overdose deaths have become a significant public health concern both nationally and in Oklahoma. From 1999 to 2012, drug overdose deaths increased eightfold in Oklahoma and since 2013 have exceeded the number of fatalities due to auto accidents. In a May 2017 editorial, Oklahoma Attorney General, Mike Hunter, estimated the number of opioid-related overdose deaths in Oklahoma to be 2,684 over the past three years, with the caveat that the actual figure could be higher. In April 2017, the Cherokee Nation filed a lawsuit against opioid wholesalers and pharmacies including Wal-Mart, CVS, and Walgreens, alleging the companies haven't done enough to prevent tribal members from obtaining inappropriately prescribed painkillers. Similar lawsuits are being filed across the country. Additionally, states are filing lawsuits against pharmaceutical companies who manufacture opioids for their alleged role in exacerbating the opioid epidemic.

Background[6,7]

In March 2016, the Centers for Disease Control and Prevention (CDC) released guidelines for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guidelines outlined 12 recommendations based on the following assessments:

- No evidence shows long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least one year later.
- Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

Morphine is considered the “gold standard” for the treatment of pain, and is used as the basis for comparison via morphine milligram equivalent (MME). The MME provides a conversion factor for one opioid to another and gives a standard for comparison. The CDC recommends clinicians prescribe the lowest effective opioid dosage when a patient begins opioid therapy for chronic pain, and encourages caution for doses exceeding 50 MME per day and avoidance of doses exceeding 90 MME per day.

Oklahoma Health Care Authority (OHCA) Opioid Initiatives[8,9,10,11,12]

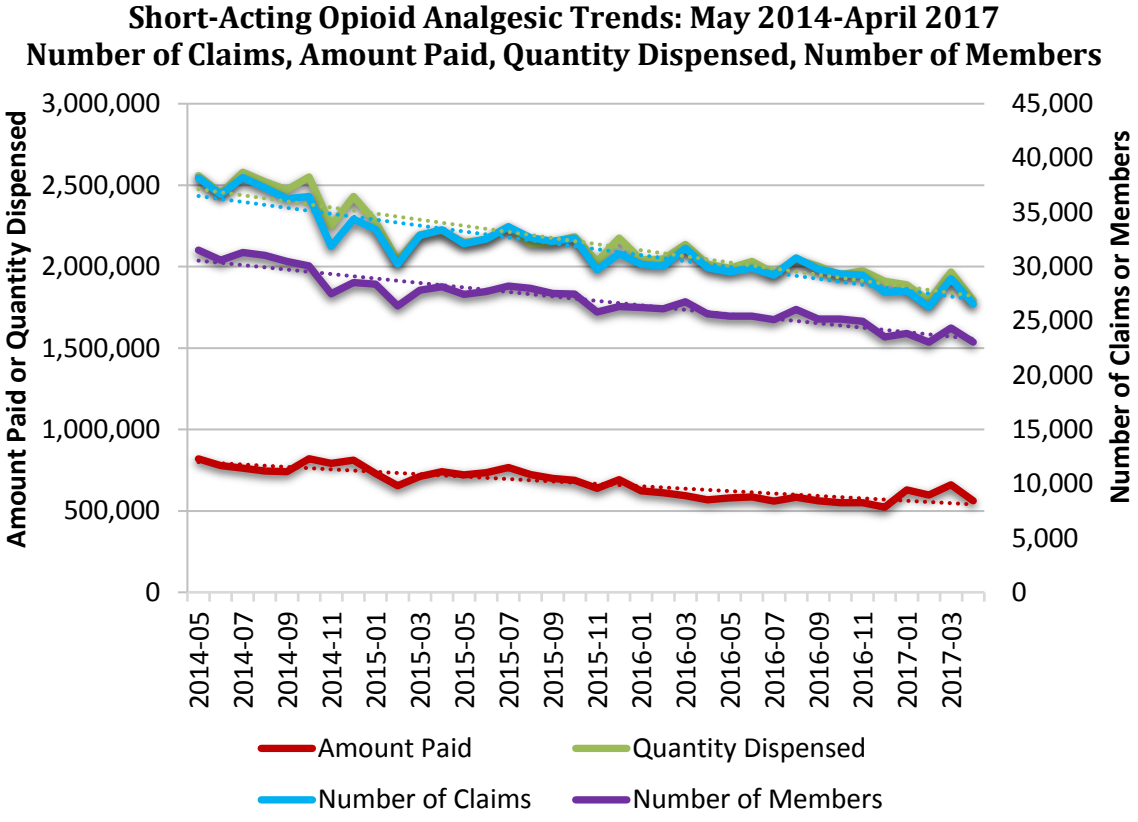
The Oklahoma Health Care Authority (OHCA) is committed to curbing the opioid epidemic and is continually monitoring SoonerCare utilization of opioid analgesics. In addition to monitoring, the OHCA has been active in curbing opioid abuse and overdose deaths as demonstrated by the following:

- In 2014, the OHCA partnered with the OU College of Pharmacy in implementing the "No More than 4" campaign which restricts the amount of short-acting opioid analgesics paid per claim to 120 tablets or capsules per 30 day supply.
- In 2014, the SoonerCare Lock In program, which requires members with history of abuse or inappropriate utilization of controlled medications to be "locked in" to a single designated pharmacy, extended the Lock In program to include a single designated prescriber of controlled medications for each member. Members are still able to receive non-controlled medications through multiple prescribers and pharmacies.
- In 2015, the OHCA negotiated supplemental rebate contracts with manufacturers of abuse-deterrent opioid analgesic products to allow for cost-effective placement of abuse-deterrent formulations in Tier-1 and Tier-2 of the opioid analgesic tier structure thereby increasing access to abuse-deterrent formulations.
- In September 2016, the Drug Utilization Review (DUR) board voted to move methadone from Tier-1 to Tier-3 of the opioid analgesic tier structure. The move was a result of several studies indicating the increased risk of overdose death associated with methadone compared to other opioid analgesics.
- The SoonerCare Pain Management Program is a program designed to equip SoonerCare providers with the knowledge and skills to appropriately treat members with chronic pain. To accomplish this, the OHCA has developed a proper prescribing toolkit. Two practice facilitators have been delegated to implement the components of the toolkit within selected SoonerCare practices. Additionally, two behavioral health resource specialists are dedicated to assist providers with linking members with substance use disorder or other behavioral health needs to the appropriate treatment.
- The OHCA has partnered with the Oklahoma Department of Mental Health and Substance Abuse Services (ODMHSAS) to increase access to naloxone. Funds received from the Health Services Initiative – Children's Health Insurance Program (CHIP) help to provide this lifesaving drug to at-risk youth through the Opioid Overdose and Naloxone Distribution (OEND) Program. OEND makes naloxone available, at no charge, to any individual 19 years of age or younger and to anyone who knows a youth who is at risk of overdose in 13 high-need Oklahoma counties.
- The OHCA is in the process of incorporating the use of MME for all opioids into the Medicaid Management Information System (MMIS), the claims processing and informational retrieval agent utilized by SoonerCare. Overlapping opioid claims will be totaled to include a member's aggregate MME per day.
- The OHCA is in the process of reviewing members who have been locked in to a single designated pharmacy and prescriber but continue to receive prescriptions for controlled drugs through unapproved pharmacies and/or prescribers via cash payments. These members have been warned that they could lose their SoonerCare benefits and have been referred to the OHCA behavioral health unit.
- The OHCA has partnered with the OU College of Pharmacy in providing opioid education to providers via numerous provider newsletter articles and educational mailings including updates on the "No More than 4" campaign, naloxone access, and opioid safety alerts.

- In June 2017, the OHCA sent letters to the top 10 prescribers of hydrocodone, oxycodone, and alprazolam. The OHCA will monitor feedback from these prescribers, and a review of the process will be conducted.

Opioid Claims Analysis

In July of 2013, the DUR board voted to reduce the number of immediate-release opioid units per claim resulting in a maximum quantity of 120 units per 30 day supply. In November of 2014, the College of Pharmacy and the OHCA began implementation of a quantity reduction on all immediate-release, solid dosage form opioid analgesics. The quantity limit was phased in over a three month period and was fully implemented by the end of January 2015. The following chart shows the utilization trends of immediate-release, solid dosage formulation opioid analgesics. All parameters have followed a linear decline since implementation of the quantity limit; linear trends are noted in the chart by dotted lines for each parameter. Additionally, the number of monthly prescribers of short-acting opioid analgesic decreased by 16% since 2014. (*Of note, hydrocodone became a Schedule II medication 10/06/2014; mandatory prescription monitoring program (PMP) check implemented 11/01/2015 for prescribers of opioids to new patients or after 180 days elapsed since PMP check).*



The OHCA has evaluated members who have opioid claims by multiple prescribers through multiple pharmacies following the mandatory PMP check implemented November 1, 2015. The number of multiple prescriber episodes in this population has decreased by approximately 50% since that time.

Next Steps

The OHCA plans to supply MME values for each opioid drug in the MMIS drug reference file; this information can then be used for the review of prescribing patterns and implementation of claims edits. The following are proposed claims review activities to be done in three (3) phases:

- **Phase 1:** Return the calculated total daily MME dose a member is receiving based on retrospective and prospective claims review at the point of service (POS) via claims messaging.
- **Phase 2:** Establish MME limits and review claims based on pre-established guidelines for MME. Audit claims and report and monitor for quality improvement and next steps.
- **Phase 3:** Provide prescribers with their daily MME via official communications. Identify top MME prescribers for quality assurance and program integrity review.

Future planned letters from the OHCA include a mailing to prescribers whose patients have had four prescriber claims and four prescription claims for opioids and/or benzodiazepines in 90 days.

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Appendix C

Vote to Prior Authorize Austedo™ (Deutetrabenazine) and Xenazine® (Tetrabenazine)

Oklahoma Health Care Authority
July 2017

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

Huntington's disease (HD) is a hereditary, progressive neurodegenerative disorder characterized by choreiform movements, psychiatric symptoms, and dementia. HD is inherited in an autosomal dominant fashion meaning every child of an affected parent has a 50% chance of developing the disease. The diagnosis of HD is normally based on the presence of typical clinical features and a family history of the disease.

Motor symptoms are a key feature of HD and include chorea and the impairment of voluntary movements. Chorea is a sudden, involuntary, arrhythmic movement; chorea is more prominent in the upper extremities early in the disease but as the disease progresses chorea may include the face, trunk, and legs. Chorea typically increases in frequency and amplitude as the disease progresses with a peak approximately 10 years after disease onset. In late HD, chorea may decline and be replaced by a parkinsonian akinetic-rigid state. HD is also associated with an increased suicide risk, which may be as high as 20% among HD mutation carriers and 7% among affected individuals.

Current guidelines for the treatment of chorea in HD recommend Xenazine® (tetrabenazine), amantadine, or riluzole. Austedo™ (deutetrabenazine) has not yet been evaluated for incorporation into the HD chorea treatment guidelines. Of the three recommended therapies, tetrabenazine is the only U.S. Food and Drug Administration (FDA) approved therapy for the treatment of chorea in HD, and the only therapy found to be likely effective in decreasing HD chorea to a very important degree. It is important to note that although the Unified Huntington's Disease Rating Scale (UHDRS) is the main outcome measure for HD studies, a "clinically important change on the UHDRS remains undefined." [5]

Cost Comparison:

Medication	Maximum Daily Dose	Cost per Unit	Cost per Day	Cost per 30 Days
Austedo™ (deutetrabenazine) 12mg	48mg	$82.20	$328.80	$9,864.00
Xenazine® (tetrabenazine) 25mg	100mg	$208.46	$833.84	$25,015.20*
tetrabenazine 25mg	100mg	$126.09	$504.36	$15,130.80

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.
*FDA approved in 2008 and has a significant rebate.

Xenazine® (Tetrabenazine) Off-Label Uses[6,7,8]

The Centers for Medicare and Medicaid Services (CMS) specifies a list of compendia approved for use in determining a "medically-accepted indication" of an off-label drug. Thompson Micromedex DrugDex® is considered an approved compendia for this use. Off-label or non-FDA approved indications that DrugDex® lists as "Class I, Class IIa, or Class IIb" recommendations and/or efficacy are considered medically accepted indications for the purposes of determining coverage policies. IIb is the lowest level of accepted recommendations for off-label use, and is described as "recommended in some cases" and "the given treatment may be useful and is indicated in some, but not most cases."[7] The following table contains off-label uses of tetrabenazine with a recommendation rating of IIb or better. Other vesicular monoamine transporter-2 (VMAT2) inhibitors are pursuing these indications.

Off-Label Uses of Tetrabenazine		
	Tardive Dyskinesia (TD)	**Tourette Syndrome**
Compendia Recommendation Level	Adult: IIb	Adult: IIb, Pediatric: IIb
Compendia Summary	"Effective in 50% or more of patients in several studies"[8] "Good efficacy in patients unresponsive to prior regimens"[8]	"Good response observed in up to one-third of patients in uncontrolled studies"[8]
Compendia Cited Studies	• Placebo-controlled study, of 6 patients: tetrabenazine 25mg 2 to 4 times daily for 1 week eliminated phenothiazine-induced facial dyskinesia in half of patients; dyskinesias returned within days of discontinuing tetrabenazine • Tetrabenazine 25mg to 200mg divided daily for a mean of 21 months in 44 TD patients: resulted in a marked reduction in abnormal movements (with excellent functional improvement) in 14% of patients; 57% demonstrated moderate reduction of abnormal movements and good functional improvement	• Tetrabenazine 37.5mg to 150mg for a mean of 14 months in an open trial of 17 patients with a mean age of 20 years (range 1 to 59 years): marked reduction in abnormal movements (with excellent functional improvement) in one patient (6%); 4 patients (23%) demonstrated moderate reduction of abnormal movements (good improvement in function); fair response in 65% of patients

Recommendations

The College of Pharmacy recommends the prior authorization of Xenazine® (tetrabenazine) and Austedo™ (deutetrabenazine) with the following criteria:

Xenazine® (Tetrabenazine) Approval Criteria:

1. Authorization of generic tetrabenazine (in place of brand Xenazine®) will require a patient-specific, clinically significant reason why the member cannot use the brand formulation (brand formulation is preferred); and
2. A diagnosis of one of the following:
    a. Chorea associated with Huntington's disease; or
    b. Tardive dyskinesia; or
    c. Tourette syndrome; and
3. Xenazine® must be prescribed by a neurologist, or a mid-level practitioner with a supervising physician that is a neurologist; and
4. Member must not be actively suicidal or have uncontrolled depression and prescriber must verify member will be monitored for depression prior to starting Xenazine® therapy and throughout treatment; and
5. Member must not have hepatic impairment; and
6. Member must not be taking monoamine oxidase inhibitors (MAOIs) or have taken an MAOI within the last 14 days; and
7. Member must not be taking reserpine or have taken reserpine within the last 20 days; and
8. Member must not use another vesicular monoamine transporter-2 (VMAT2) inhibitor (e.g., deutetrabenazine, valbenazine) concurrently with Xenazine®; and
9. Member must not be taking medications that are known to prolong the QTc interval concomitantly with Xenazine® [antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, or any other medications known to prolong the QTc interval]; and
10. Patients who require doses of tetrabenazine greater than 50mg per day must be tested and genotyped to determine if they are poor metabolizers (PMs), intermediate metabolizers (IMs), or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The following dose limits will apply based on patient metabolizer status:
    a. Extensive and Intermediate CYP2D6 Metabolizers: 100mg divided daily; or
    b. Poor CYP2D6 Metabolizers: 50mg divided daily; and
11. The daily dose of Xenazine® must not exceed 50mg per day if the member is taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion); and
12. Approvals will be for the duration of six months at which time the prescriber must document that the signs and symptoms of chorea, tardive dyskinesia, or Tourette syndrome have decreased and the member is not showing worsening signs of depression.

Austedo™ (Deutetrabenazine) Approval Criteria:

1. An FDA approved diagnosis of chorea associated with Huntington's disease; and
2. Austedo™ must be prescribed by a neurologist, or a mid-level practitioner with a supervising physician that is a neurologist; and
3. A previous trial of Xenazine® (tetrabenazine) or a patient-specific, clinically significant reason why the member cannot use brand Xenazine® (tetrabenazine); and
4. Member must not be actively suicidal or have uncontrolled depression and prescriber must verify member will be monitored for depression prior to starting Austedo™ therapy and throughout treatment; and
5. Member must not have hepatic impairment; and
6. Member must not be taking monoamine oxidase inhibitors (MAOIs) or have taken an MAOI within the last 14 days; and
7. Member must not be taking reserpine or have taken reserpine within the last 20 days; and
8. Member must not use another vesicular monoamine transporter-2 (VMAT2) inhibitor (e.g., tetrabenazine, valbenazine) concurrently with Austedo™; and
9. Member must not be taking medications that are known to prolong the QTc interval concomitantly with Austedo™ [antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, or any other medications known to prolong the QTc interval]; and
10. The daily dose of Austedo™ must not exceed 36mg per day if the member is taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion) or if they are a known poor CYP2D6 metabolizer; and
11. Approvals will be for the duration of six months at which time the prescriber must document that the signs and symptoms of chorea have decreased and the member is not showing worsening signs of depression.

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Appendix D

Vote to Update the Inhaled Tobramycin Products, Pulmozyme® (Dornase Alfa), and Cayston® (Aztreonam) Prior Authorization Criteria

Oklahoma Health Care Authority
July 2017

Introduction

When the Drug Utilization Review (DUR) board voted to prior authorize the inhaled tobramycin products in February 2014, access to Tobi® Podhaler™ was voted to remain similar to nebulized tobramycin with the recommendation that a study be conducted to evaluate and compare the impact of the two products on overall healthcare outcomes including hospitalizations and pharmacy costs. Faculty at the College of Pharmacy performed the study, the results of which were presented at the October 2015 DUR board meeting. Net costs were similar during fiscal year 2016 and all products were recommended to be treated with similar criteria. With the U.S. Food and Drug Administration (FDA) approval of several generic formulations of nebulized tobramycin, net costs no longer remain similar and further review among the formulations is warranted.

Resource Evaluation of Tobramycin Formulations in a State Medicaid Program
Shellie Keast, Pharm.D., Ph.D., Assistant Professor, University of Oklahoma College of Pharmacy

Research was a longitudinal, historical cohort study designed to follow CF patients for 12 months after a switch between inhaled tobramycin formulations. The outcomes assessed included adherence to tobramycin therapy, utilization of non-tobramycin anti-*pseudomonal* antibiotics, respiratory related hospitalizations, and pharmacy and medical costs, reported as per member per eligible month (PMPM). The switch period was defined as May 1, 2013 through April 30, 2014 and a total of 54 patients were included in the study after meeting all inclusion criteria and matching for independent variables (dry powder [DP] = podhaler formulation; solution [SOL] = nebulized formulation).

- Anti-*pseudomonal* antibiotic reimbursement PMPM was significantly different with higher reimbursement for the DP group compared to the SOL group ($1,095 vs $577, $p<0.001$).
- Inpatient hospitalization reimbursement PMPM for the DP group was lower than for the SOL group and was statistically significant ($503, $p=0.031$).
- The proportion of members considered adherent to tobramycin therapy was higher for the DP group (55.6%) compared to the SOL group (44.4%), but this was not statistically significant ($p=0.457$). There was no difference in odds of being adherent between groups (AOR 1.661; $p=0.366$).

Tobramycin Formulation	Tobramycin PMPM	Anti-*pseudomonal* Antibiotic PMPM	Inpatient PMPM	Proportion Members Adherent
Dry Powder	$3,394	$1,095*	$212*	55.6%
Solution	$2,387	$577*	$714*	44.4%

PMPM = per member per eligible month, *indicates statistically significant

Cost Comparison:

Medication	Cost per Unit	Dosing	Cost per 28 Days of Therapy
Tobi® Podhaler™ (tobramycin powder inhalation)	$42.69	4 capsules BID	$9,562.56
tobramycin nebulized solution	$11.41	300mg/5mL BID	$3,194.80
Bethkis® (tobramycin nebulized solution)	$25.33	300mg/4mL BID	$5,673.92
Kitabis™ Pak (tobramycin nebulized solution)	$16.07	300mg/5mL BID	$4,499.60

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 = capsule or milliliter; mL = milliliter; BID = twice daily

Estimated Annual Savings:

- If all members utilizing Tobi® Podhaler™ during calendar year 2016 switched to generic tobramycin nebulized solution, the estimated annual pharmacy savings would be $369,330.08. This estimation does not account for rebated prices or net costs.

Recommendations

The College of Pharmacy recommends the following changes noted in red to the inhaled tobramycin product prior authorization criteria:

Inhaled Tobramycin Products (Bethkis®, Tobi®, Tobi® Podhaler™, and Kitabis™ Pak), Pulmozyme® (Dornase Alfa), & 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.
   a. Authorization of Bethkis®, Tobi® Podhaler™, and Kitabis™ Pak 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, 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 cystic fibrosis within the past 12 months of claims history.
   c. If the member does not have a reported 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.

Appendix E

Vote to Prior Authorize Ingrezza™ (Valbenazine)

Oklahoma Health Care Authority
July 2017

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

Tardive dyskinesia (TD) is an involuntary neurological movement disorder that appears with a delayed onset after prolonged use of dopamine receptor blocking agents (DRBAs), primarily antipsychotic medications and the antiemetic drug, metoclopramide. Prevention of TD, as well as early detection and treatment of potentially reversible cases of TD are of utmost importance. Initial treatment of TD includes discontinuing the causative medication if possible. If a patient who develops signs of TD requires continued treatment, switching to a medication with less potent dopamine receptor (D2) blockade may be attempted, but all DRBAs carry a risk of TD. In April 2017, the U.S. Food and Drug Administration (FDA) approved Ingrezza™ (valbenazine), a selective vesicular monoamine transporter 2 (VMAT2) inhibitor, for the treatment of adults with TD. It is the first medication approved for the treatment of TD. Prior to the approval of valbenazine, pharmacological treatment options for TD included VMAT2 inhibitors (e.g., tetrabenazine), amantadine, clonazepam, ginkgo biloba extract, and botulinum toxin.

The recommended initial dose of valbenazine is 40mg by mouth once daily. It is recommended to increase the dose after one week to 80mg once daily. The wholesale acquisition cost (WAC) of Ingrezza™ (valbenazine) is $175.83 per 40mg capsule.

Recommendations

The College of Pharmacy recommends the prior authorization of Ingrezza™ (valbenazine) with the following criteria:

Ingrezza™ (Valbenazine) Approval Criteria:

1. An FDA approved diagnosis of tardive dyskinesia meeting the following DSM-5 criteria:
    a. Involuntary athetoid or choreiform movements; and
    b. History of treatment with dopamine receptor blocking agent (DRBA); and
    c. Symptom duration lasting longer than 4 to 8 weeks; and
2. Member must be 18 years of age or older; and
3. Ingrezza™ must be prescribed by a neurologist or psychiatrist, or a mid-level practitioner with a supervising physician that is a neurologist or psychiatrist; and
4. Member must not be at significant risk for suicidal or violent behavior and must not have unstable psychiatric symptoms; and
5. The daily dose of Ingrezza™ must not exceed 40mg per day if the member is taking strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, clarithromycin); and
6. Member must not be taking monoamine oxidase inhibitors (MAOIs); and
7. Member must not be taking other vesicular monoamine transporter 2 (VMAT2) inhibitors (e.g., tetrabenazine, deutetrabenazine); and
8. Female members must not be pregnant or breastfeeding; and

9. Prescriber must document a baseline evaluation using the Abnormal Involuntary Movement Scale (AIMS); and
10. A quantity limit of two 40mg capsules or a total dose of 80mg per day will apply; and
11. Approvals will be for the duration of six months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment as indicated by an improvement from baseline in the AIMS total score (a negative change in score indicates improvement).

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Appendix F

Vote to Update the Atypical Antipsychotic Prior Authorization Criteria and Tier Chart

Oklahoma Health Care Authority
July 2017

Introduction[1,2,3]

Medicaid Drug Rebate Program: Medicaid coverage of a drug requires the manufacturer to have a **federal rebate** agreement with the Secretary of Health and Human Services (HHS). Rebate amounts are based on the "best price" for each drug. Best price refers to the lowest price paid to a manufacturer for a drug by any payer. If a drug's price increases more quickly than inflation, an additional rebate penalty is included based on the change in price compared with the consumer price index (CPI). The CPI penalty of the federal rebate is designed to keep Medicaid net cost relatively flat despite increases in drug prices and now applies to both brand and generic medications. As wholesale acquisition cost (WAC) or list price increases, the rebated amount per unit (RAPU) increases as well, resulting in minimal effect on Medicaid net cost. Additionally, many states have negotiated **supplemental rebate** agreements with manufacturers to produce added rebates. The atypical antipsychotic Product Based Prior Authorization (PBPA) category is heavily influenced by supplemental rebates. In calendar year 2016, the Oklahoma Health Care Authority (OHCA) collected $19,996,544.39 in aggregate drug rebates for atypical antipsychotic medications (*see below for comparison to calendar year 2015 costs and rebates*); these rebates are collected after reimbursement for the medication.

Calendar Year	Total Cost	Aggregated Drug Rebates	Adjusted Total Cost
2015	$55,588,255.60	$38,220,344.65	$17,367,910.95
2016	$42,762,939.44	$19,996,544.39	$22,766,395.05

Recommendations

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

1. In addition to the Tier-3 criteria requirements for consideration of Symbyax® (olanzapine/fluoxetine), approval would require a patient-specific, clinically significant reason why the member could not use olanzapine and fluoxetine as individual components, both of which are available without prior authorization.
2. The movement of Seroquel® XR (quetiapine extended-release [ER]) to Tier-1 of the Atypical Antipsychotics PBPA Tier chart once the cost is comparable to other Tier-1 generic medications.
3. A trial of Seroquel® XR (*pending Tier-1 move*) will be required for approval of Latuda® (lurasidone) for a diagnosis of bipolar depression.

4. For atypical antipsychotic Tier-2 approval consideration, a trial of any Tier-1 medication at least 14 days in duration, titrated to recommended dose that did not yield adequate response or resulted in intolerable effects will be required in place of a required aripiprazole trial.
5. In addition to the current Tier-3 criteria, a trial of any Tier-1 medication at least 14 days in duration, titrated to recommended dose that did not yield adequate response or resulted in intolerable effects will be required in place of a required aripiprazole trial.

Recommended Prior Authorization Criteria

Tier-1 products are available without prior authorization for ages five years and older. Prior authorization requests for members younger than five years of age are reviewed by an Oklahoma Health Care Authority (OHCA)-contracted child psychiatrist.

Atypical Antipsychotic Tier-2 Approval Criteria:

1. A trial of a Tier-1 medication at least 14 days in duration, titrated to recommended dose that did not yield adequate response or resulted intolerable adverse effects.
    a. Clozapine does not count towards a Tier-1 trial.

Atypical Antipsychotic Tier-3 Approval Criteria:

1. A trial of a Tier-1 medication at least 14 days in duration, titrated to recommended dose that did not yield adequate response or resulted intolerable adverse effects; and
    a. Clozapine does not count towards a Tier-1 trial; and
2. Trials of all oral Tier-2 medications, at least 14 days in duration each, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects; or
3. A manual prior authorization may be submitted for consideration of a Tier-3 medication when the member has had at least four trials of Tier-1 and Tier-2 products (two trials must be from Tier-1) that did not yield an adequate response or resulted in intolerable adverse effects; and
4. Use of Versacloz™ (clozapine oral suspension) and Fazaclo® (clozapine orally disintegrating tablet) requires a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation.

Approval Criteria for Atypical Antipsychotics as Adjunctive Treatment for Major Depressive Disorder:

1. Authorization of Seroquel XR® (quetiapine extended-release), Symbyax® (olanzapine/fluoxetine), or Rexulti® (brexpiprazole) for a diagnosis of major depressive disorder requires current use of an antidepressant, and previous trials with at least two other antidepressants from both categories (an SSRI and duloxetine) and a trial of aripiprazole tablets that did not yield adequate response. Tier structure applies.

Atypical Antipsychotics*		
Tier-1	**Tier-2**	**Tier-3**
aripiprazole (Abilify®)[¥]	aripiprazole (Abilify Maintena®)	brexpiprazole (Rexulti®)
clozapine (Clozaril®)[◊]	aripiprazole lauroxil (Aristada®)	cariprazine (Vraylar™)
olanzapine (Zyprexa®)	asenapine (Saphris®)	clozapine (Fazaclo®)
quetiapine (Seroquel®)		clozapine oral suspension (Versacloz™)
quetiapine ER (Seroquel XR®)**	**lurasidone (Latuda®)[±]**	iloperidone (Fanapt®)
risperidone (Risperdal®)	paliperidone (Invega® Sustenna®)	**olanzapine/fluoxetine (Symbyax®)[α]**
risperidone (Risperdal Consta®)	paliperidone (Invega® Trinza™)[∞]	paliperidone (Invega®)
ziprasidone (Geodon®)		

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

*Mandatory generic plan applies

[◊]Does not count toward a Tier-1 trial

[∞]In addition to tier trials, use of Invega® Trinza™ requires members to have been adequately treated with the 1-month paliperidone extended-release injection (Invega® Sustenna®) for at least four months.

[¥]Aripiprazole (Abilify®) orally disintegrating tablets (ODT) are considered a special formulation and will require a patient-specific, clinically significant reason why a special formulation product is needed in place of the regular tablet formulation. Aripiprazole oral solution for members older than seven years of age requires a patient-specific, clinically significant reason why the oral tablet formulation cannot be used. Aripiprazole oral solution will not require prior authorization for ages five to seven years of age. Prior authorization requests for members younger than five years of age are reviewed by an OHCA-contracted child psychiatrist.

**Seroquel® XR (quetiapine ER) move to Tier-1 dependent on generic cost.

[±] Latuda® (lurasidone) requires a trial of Seroquel® XR (quetiapine ER) (*pending Tier-1 move*) for a diagnosis of bipolar depression.

[α] In addition to the Tier-3 criteria requirements, approval requires a patient-specific, clinically significant reason why the member cannot use olanzapine and fluoxetine as individual components.

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[1] Peters CP. The Basics: The Medicaid Drug Rebate Program. *National Health Policy Forum*. Available online at: https://www.nhpf.org/library/the-basics/Basics_MedicaidDrugRebate_04-13-09.pdf. Issued 04/13/2009. Last accessed 05/23/2017.

[2] Office of Inspector General. Department of Health and Human Services. States' Collection of Offset and Supplemental Medicaid Rebates. Available online at: http://oig.hhs.gov/oei/reports/oei-03-12-00520.pdf. Last revised 12/2014. Last accessed 05/23/2017.

[3] Gibbons DC, Kirschenbaum AM. Bipartisan Budget Bill Extends Medicaid Drug Rebate Program Price Increase Penalty to Generic Drugs. *FDA Law Blog*. Available online at: http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/11/bipartisan-budget-bill-extends-medicaid-drug-rebate-program-price-increase-penalty-to-generic-drugs.html. Issued 11/02/2015. Last accessed 05/23/2017.

Appendix G

Vote to Prior Authorize Carac® (Fluorouracil 0.5% Cream), GoNitro™ (Nitroglycerin Sublingual Powder), Soltamox® (Tamoxifen Citrate Oral Solution), Taytulla™ (Norethindrone Acetate/Ethinyl Estradiol Capsules & Ferrous Fumarate Capsules), Tirosint®-SOL (Levothyroxine Sodium Oral Solution), Xatmep™ (Methotrexate Oral Solution), Zovirax® (Acyclovir Ointment & Suspension), Xerese® (Acyclovir/Hydrocortisone Cream), & Denavir® (Penciclovir Cream)

Oklahoma Health Care Authority
July 2017

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

Carac® (fluorouracil 0.5% cream) is an antineoplastic agent indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp in adults. Carac® is available as a topical 0.5% fluorouracil cream, with 0.35% being incorporated into a patented porous microsphere (Microsponge®). It is supplied in a 30g tube. It should be applied once a day for up to four weeks.

- Other Formulation(s) Available: fluorouracil 5% cream, fluorouracil 5% solution, and fluorouracil 2% solution

Formulation Cost Comparison:

Product	Cost Per Gram or mL	Cost Per Treatment
Carac® (fluorouracil 0.5% cream)	**$80.16**	**$2,404.80**
fluorouracil 0.5% cream	**$48.47**	**$1,454.10**
fluorouracil 5% cream	$3.02	$120.80
fluorouracil 5% solution	$5.56	$55.60
fluorouracil 2% solution	$4.48	$44.80

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.

GoNitro™ (nitroglycerin sublingual powder) is a nitrate vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease. GoNitro™ is available in a packet containing 400mcg of sublingual nitroglycerin powder. It should be administered as one or two packets under the tongue at the onset of an attack. One additional packet may be administered every 5 minutes as needed. No more than three total packets (1,200mcg) are recommended within a 15 minute period. If the chest pain persists after three packets, prompt medical attention is advised. GoNitro™ may be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack.

- Other Formulation(s) Available: nitroglycerin sublingual tablets and nitroglycerin lingual spray

Formulation Cost Comparison:

Product	Cost Per Dose or Gram	Cost Per Package
GoNitro™ (nitroglycerin sublingual powder)	**$6.81**	**$81.72 - $653.76**
nitroglycerin sublingual tablets	$0.33 - $0.58	$33.00 - $58.00
nitroglycerin lingual spray	$19.68 - $35.20	$172.40 - $236.16

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

Soltamox® (tamoxifen citrate 10mg/5mL oral solution) is a nonsteroidal selective estrogen receptor modulator (SERM) indicated for the following: treatment of metastatic breast cancer in women and men, adjuvant treatment of node-positive breast cancer in postmenopausal women and for the adjuvant treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation, the reduction in risk of invasive breast cancer in women with ductal carcinoma *in situ* (DCIS), following breast surgery and radiation, or to reduce the incidence of breast cancer in women at high risk for breast cancer. Soltamox® is available as a sugar-free, clear, colorless liquid containing 10mg of tamoxifen in each 5mL of solution. For patients with breast cancer, the recommended daily dose is 20mg to 40mg. For DCIS and reduction in breast cancer incidence in high-risk women, the recommended dose is 20mg daily for 5 years.

- Other Formulation(s) Available: tamoxifen citrate 10mg and 20mg tablets

Formulation Cost Comparison:

Product	Cost Per Tablet or mL	Cost for 30 Days
Soltamox® (tamoxifen citrate oral solution)	**$3.82**	**$1,146.00 - $2,292.00**
tamoxifen citrate 10mg tablets	$0.25	$15.00 - $30.00
tamoxifen citrate 20mg tablets	$0.53	$15.90 - $31.80

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.

Taytulla™ (norethindrone acetate/ethinyl estradiol capsules and ferrous fumarate capsules) is an estrogen/progestin combination oral contraceptive (COC) indicated for use by women to prevent pregnancy. Taytulla™ is available in blister packs containing 24 soft gelatin capsules of 1mg norethindrone and 20mcg ethinyl estradiol, and 4 capsules of 75mg ferrous fumarate. The recommended dosing is one capsule at the same time every day.

- Other Formulation(s) Available: various generic formulations of norethindrone acetate/ethinyl estradiol tablets with ferrous fumarate tablets (Loestrin®24 Fe)

Formulation Cost Comparison:

Product	Cost Per Tablet or Capsule	Cost Per Pack
Taytulla™ (norethindrone acetate/ethinyl estradiol capsules & ferrous fumarate capsules)	**$5.37**	**$150.36**
norethindrone acetate/ethinyl estradiol 1mg/20mcg tablets & ferrous fumarate tablets	$1.26	$35.28

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.

Tirosint®-SOL (levothyroxine sodium oral solution) is L-thyroxine (T_4) indicated for hypothyroidism and pituitary thyrotropin (thyroid-stimulating hormone, TSH) suppression. Tirosint®-SOL is supplied as a clear, colorless to slightly yellow solution in a 1mL white, non-transparent, unit-dose ampule, and is available in 12 strengths ranging from 13mcg to 200mcg. The recommended dosing is once daily, on an empty stomach.

- Other Formulation(s) Available: levothyroxine sodium tablets

Formulation Cost Comparison:

Product	Cost Per Tablet or mL	Cost for 30 Days
Tirosint®-SOL (levothyroxine sodium oral solution)	**Unknown**	**Unknown**
Synthroid® (levothyroxine sodium tablets)	$1.08 - $1.16	$32.40 - $34.80
levothyroxine sodium tablets	$0.30 - $0.76	$9.00 - $22.80

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.

Xatmep™ (methotrexate 2.5mg/mL oral solution) is a folate analog metabolic inhibitor indicated for the following: treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen or management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy. Xatmep™ is available as a clear yellow to orange oral solution that contains 2.5mg of methotrexate per milliliter. The recommended dosing is for ALL is 20mg/m^2 one time weekly. The starting dose for pJIA is 10mg/m^2 one time weekly.

- Other Formulation(s) Available: methotrexate tablets, methotrexate injection solution, and Trexall® tablets

Formulation Cost Comparison:

Product	Cost Per Tablet or mL	Cost for 30 Days$^{\Delta}$
Xatmep™ (methotrexate oral solution)	**$15.80**	**$189.60**
Trexall® (methotrexate tablet) 7.5mg	$19.95	$79.80*
methotrexate injection solution	$1.45	$11.60^{+}
methotrexate tablet 2.5mg	$1.04	$12.48

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.

$^{\Delta}$Cost for 30 days based on pJIA weekly dosing of 10mg/m^2 for a child weighing 18.6kg and 109.2cm tall.

*FDA approved in 2001 and has a significant rebate.

$^{+}$Cost for 30 days of methotrexate injection solution based on use of a 2mL single-use vial for each weekly dose

Zovirax® (acyclovir 5% ointment) is a synthetic nucleoside analogue indicated in the management of initial genital herpes simplex virus (HSV) and in limited non-life-threatening mucocutaneous HSV infections in immunocompromised patients. Zovirax® ointment is supplied in a 30g tube containing 50mg of acyclovir per gram. The recommended dosing is topical application of a sufficient quantity to adequately cover all lesions every 3 hours, 6 times per day for 7 days**.**

Zovirax® (acyclovir 200mg/5mL suspension) is indicated for the acute treatment of herpes zoster (shingles), initial episodes and the management of recurrent episodes of genital herpes,

and chickenpox (varicella). Zovirax® suspension is supplied as an off-white, banana-flavored oral suspension containing 200mg of acyclovir per 5mL. Dosing varies depending on diagnosis.

Xerese® (acyclovir/hydrocortisone 5%/1% cream) is a combination of a nucleoside analog and a corticosteroid. It is indicated for the early treatment of recurrent HSV labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and children (6 years of age and older). Xerese® is supplied in a 5g tube containing 5% acyclovir and 1% hydrocortisone per gram. The recommended dosing is topical application 5 times a day for 5 days.

Denavir® (penciclovir 1% cream) is a nucleoside analog indicated for the treatment of recurrent HSV labialis (cold sores) in adults and children (12 years of age and older). Denavir® is supplied in 1.5g and 5g tubes containing 10mg of penciclovir per gram. The recommended dosing is topical application every 2 hours during waking hours for a period of 4 days.

- Other Formulation(s) Available: acyclovir tablets, acyclovir capsules, and Zovirax® (acyclovir 5%) cream

Formulation Cost Comparison:

Product	Cost Per Tablet/Capsule or Gram	Cost for Treatment[+]
Zovirax® (acyclovir 5% ointment)	**$8.56**	**$256.80**
Xerese® (acyclovir/hydrocortisone 5%/1% cream)	**$225.47**	**$1,127.35**
Denavir® (penciclovir 1% cream)	**$143.08**	**$715.40**
Zovirax® (acyclovir 5% cream)	$140.34	$701.70[Δ]
acyclovir tablets	$0.09	$2.70
acyclovir capsules	$0.11	$5.50

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.
[+]Cost per treatment based on usual dosing regimen for HSV or one tube of topical product.
[Δ]Zovirax® (acyclovir 5% cream) has a significant rebate.

Recommendations

The College of Pharmacy recommends the prior authorization of Carac® (fluorouracil 0.5% cream), GoNitro™ (nitroglycerin sublingual powder), Soltamox® (tamoxifen citrate oral solution), Taytulla™ (norethindrone acetate/ethinyl estradiol capsules & ferrous fumarate capsules), Tirosint®-SOL (levothyroxine sodium oral solution), Xatmep™ (methotrexate oral solution), Zovirax® (acyclovir ointment and suspension), Xerese® (acyclovir/hydrocortisone cream), and Denavir® (penciclovir cream) with the following criteria:

Carac® (Fluorouracil 0.5% Cream) Approval Criteria:

1. An FDA approved diagnosis of multiple actinic or solar keratoses of the face and anterior scalp in adults; and
2. Carac® must be prescribed by a dermatologist or an advanced care practitioner with a supervising physician who is a dermatologist; and
3. A patient-specific, clinically significant reason why the member cannot use fluorouracil 5% cream, fluorouracil 5% solution, or fluorouracil 2% solution.

GoNitro™ (Nitroglycerin Sublingual Powder) Approval Criteria:

1. An FDA approved indication of acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease; and
2. A patient-specific, clinically significant reason why the member cannot use nitroglycerin sublingual tablets or nitroglycerin lingual spray.

Soltamox® (Tamoxifen Citrate 10mg/5mL Oral Solution) Approval Criteria:

1. An FDA approved indication of one of the following:
    a. Treatment of metastatic breast cancer in women and men; or
    b. Adjuvant treatment of node-positive breast cancer in postmenopausal women and for the adjuvant treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation; or
    c. The reduction in risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS), following breast surgery and radiation; or
    d. To reduce the incidence of breast cancer in women at high risk for breast cancer; and
2. A patient-specific, clinically significant reason why the member cannot use tamoxifen tablets.

Taytulla™ (Norethindrone Acetate/Ethinyl Estradiol Capsules & Ferrous Fumarate Capsules) Approval Criteria:

1. An FDA approved indication to prevent pregnancy in women; and
2. A patient-specific, clinically significant reason why the member cannot use all other generic formulations of norethindrone acetate/ethinyl estradiol tablets with ferrous fumarate tablets.

Tirosint®-SOL (Levothyroxine Sodium Oral Solution) Approval Criteria:

1. An FDA approved diagnosis of one of the following:
    a. Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism; or
    b. Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer; and
2. A patient-specific, clinically significant reason why the member cannot use all other formulations of levothyroxine sodium in the place of oral solution even when tablets are crushed.

Xatmep™ (Methotrexate 2.5mg/mL Oral Solution) Approval Criteria:

1. An FDA approved indication of one of the following:
    a. Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen; or
    b. Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy; and

2. A patient-specific, clinically significant reason why the oral tablets or generic injectable formulation cannot be used.

Zovirax® (Acyclovir 5% Ointment) Approval Criteria:

1. An FDA approved indication of management of initial genital herpes or in limited non-life-threatening mucocutaneous herpes simplex virus (HSV) infections in immunocompromised patients; and
2. A patient-specific, clinically significant reason why the member cannot use oral acyclovir, famciclovir, or valacyclovir tablets.

Zovirax® (Acyclovir 200mg/5mL Suspension) Approval Criteria:

1. An age restriction of seven years and younger will apply. Members older than seven years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.

Sitavig® (Acyclovir Buccal Tablets), Xerese® (Acyclovir/Hydrocortisone 5%/1% Cream), and Denavir® (Penciclovir 1% Cream) Approval Criteria:

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

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[1] Carac® Prescribing Information. Valeant Pharmaceuticals North America, LLC. Available online at: http://valeant.com/Portals/25/Pdf/PI/Carac-PI.pdf. Last revised 11/2015. Last accessed 06/08/2017.

[2] GoNitro™ Prescribing Information. Espero Pharmaceuticals, Inc. Available online at: http://gonitropowder.com/wp-content/uploads/2016/11/GoNitro-PI-for-Print.pdf. Last revised 06/2016. Last accessed 06/08/2017.

[3] Soltamox® Prescribing Information. Rosemont Pharmaceuticals, Ltd. Available online at: http://soltamox.com/wp-content/uploads/2016/07/Soltamox-FDA-Approved-Package-Insert.pdf. Last revised 08/2012. Last accessed 06/08/2017.

[4] Taytulla™ Prescribing Information. Allergan USA, Inc. Available online at: https://www.allergan.com/assets/pdf/taytulla_pi.pdf. Last revised 08/2016. Last accessed 06/08/2017.

[5] Tirosint®-SOL Prescribing Information. U.S. Food and Drug Administration (FDA). Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206977s000lbl.pdf. Last revised 12/2016. Last accessed 06/08/2017.

[6] Xatmep™ Prescribing Information. Silvergate Pharmaceuticals, Inc. Available online at: http://silvergatepharma.com/wp-content/uploads/2017/04/PI-4-26-17.pdf. Last revised 04/2017. Last accessed 06/13/2017.

[7] National Institute of Health. Zovirax® (Acyclovir Ointment). *U.S. National Library of Medicine: DailyMed*. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=50278e0e-da1e-45ee-9fcb-672b2a219911. Last revised 01/2017. Last accessed 06/13/2017.

[8] National Institute of Health. Acyclovir Tablet, Capsule and Suspension. *U.S. National Library of Medicine: DailyMed*. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6fe0ab86-9d81-461e-9c84-6ba724a91318. Last revised 02/2014. Last accessed 06/13/2017.

[9] Xerese® Prescribing Information. Valeant Pharmaceuticals North America, LLC. Available online at: http://valeant.com/Portals/25/Pdf/PI/Xerese-PI.PDF. Last revised 01/2014. Last accessed 06/13/2017.

[10] Denavir® Prescribing Information. Prestium Pharma, Inc. Available online at: http://www.denavir.com/media/1045/denavir_pi.pdf. Last revised 09/2013. Last accessed 06/13/2017.

Appendix H

Vote to Prior Authorize Aczone® (Dapsone Gel) and Tazorac® (Tazarotene Cream and Gel)

Oklahoma Health Care Authority
July 2017

Introduction[1,2,3]

Aczone® (Dapsone Gel) is a sulfone indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

Cost Comparison:

Medication	Cost Per Gram or mL	Cost Per 30 Days of Therapy*
Aczone® (dapsone) 7.5% gel	**$8.63**	**$517.96**
Azelex® (azelaic acid) 20% cream	$12.04	$361.22◊
benzoyl peroxide 10% gel	$0.20+	$5.49+
clindamycin 1% gel	$1.75	$52.55
erythromycin 2% solution	$0.56	$33.83

Cost does not reflect rebated price or net cost. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC is unavailable.
*Cost per 30 days based on smallest package size.
◊FDA approved in 2002 and has a significant rebate.
+Cost based on Walgreens generic 28-oz tube from walgreens.com, last checked 06/16/2017.

Tazorac® (Tazarotene Cream and Gel) is a topical retinoid product indicated for topical treatment of acne vulgaris and plaque psoriasis.

Cost Comparison:

Medication	Cost Per Gram or mL	Cost Per 30 Days of Therapy*
tazarotene 0.1% cream	**$7.23**	**$216.82**
Tazorac® (tazarotene) 0.1% cream	$11.63	$348.92◊
Tazorac® (tazarotene) 0.1% gel	$11.56	$346.74◊
benzoyl peroxide 10% gel	$0.20+	$5.49+
clindamycin 1% solution	$0.68	$20.29
fluocinonide 0.05% cream	$1.08	$32.53

Cost does not reflect rebated price or net cost. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC is unavailable.
*Cost per 30 days based on smallest package size.
◊FDA approved in 1997 and has a significant rebate.
+Cost based off of Walgreens generic 28-gram tube from walgreens.com, last checked 06/16/2017.

Recommendations

The College of Pharmacy recommends the prior authorization of Aczone® (dapsone gel) and generic tazarotene cream with the following criteria based, in part, on cost after rebates:

Aczone® (Dapsone Gel) Approval Criteria:

1. An FDA approved indication of acne vulgaris; and
2. Member must be 20 years of age or younger; and
3. A previous trial of benzoyl peroxide or a patient-specific, clinically significant reason why benzoyl peroxide is not appropriate for the member; and
4. A previous trial of a topical antibiotic, such as clindamycin or erythromycin, or a patient-specific, clinically significant reason why a topical antibiotic is not appropriate for the member.

Tazorac® (Tazarotene Cream and Gel) Approval Criteria:

1. An FDA approved indication of acne vulgaris or plaque psoriasis; and
2. Female members must not be pregnant and must be willing to use an effective method of contraception during treatment; and
3. Authorization of generic tazarotene (in place of brand Tazorac®) will require a patient-specific, clinically significant reason why the member cannot use the brand formulation (brand formulation is preferred); and
4. For a diagnosis of acne vulgaris, the following must be met:
    a. Member must be 20 years of age or younger; and
5. A quantity limit of 60 grams per 30 days will apply.

[1] Aczone® 7.5% Gel Prescribing Information. Allergan, Inc. Available online at: https://www.allergan.com/assets/pdf/aczone7-5_pi. Last revised 02/2016. Last accessed 06/16/2017.
[2] Tazorac® Cream Prescribing Information. Allergan, Inc. Available online at: https://www.allergan.com/assets/pdf/tazorac_cream_pi. Last revised 12/2013. Last accessed 06/2017.
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Appendix I

Vote to Prior Authorize Vyvanse® (Lisdexamfetamine Chewable Tablets) and Update the ADHD Prior Authorization Criteria and Tier Chart

Oklahoma Health Care Authority
July 2017

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

- **Vyvanse® (lisdexamfetamine) chewable tablets** were approved by the U.S. Food and Drug Administration (FDA) in January 2017 for the treatment of ADHD in patients 6 years of age and older and for the treatment of moderate-to-severe binge eating disorder (BED) in adults. Vyvanse® capsules were first FDA approved in 2007 for the treatment of ADHD and then in 2015 for the treatment of BED. Vyvanse® capsules and chewable tablets have currently provided a supplemental rebate to be placed in Tier-1; however, Vyvanse® capsules and chewable tablets will be moved to a higher tier based on net cost in comparison to other available products if the manufacturer chooses not to participate in supplemental rebates.
- **Medicaid Drug Rebate Program:** Medicaid coverage of a drug requires the manufacturer to have a **federal rebate** agreement with the Secretary of Health and Human Services (HHS). Rebate amounts are based on the "best price" for each drug. Best price refers to the lowest price paid to a manufacturer for a drug by any payer. If a drug's price increases more quickly than inflation, an additional rebate penalty is included based on the change in price compared with the consumer price index (CPI). The CPI penalty of the federal rebate is designed to keep Medicaid net cost relatively flat despite increases in drug prices and now applies to both brand and generic medications. As wholesale acquisition cost (WAC) or list price increases, the rebated amount per unit (RAPU) increases as well, resulting in minimal effect on Medicaid net cost. Additionally, many states have negotiated **supplemental rebate** agreements with manufacturers to produce added rebates. The ADHD and Narcolepsy Medications Product Based Prior Authorization (PBPA) category is heavily influenced by supplemental rebates. The ADHD and narcolepsy brand name products that are preferred over available generic products are likely due to a lower net cost compared to generics, after taking into account rebate participation. In calendar year 2016, the Oklahoma Health Care Authority (OHCA) collected $47,627,703.84 in aggregate drug rebates for ADHD and narcolepsy medications (*see below for comparison to calendar year 2015 costs and rebates*); these rebates are collected after reimbursement for the medication.

Calendar Year	Total Cost	Aggregated Drug Rebates	Adjusted Total Cost
2015	$59,311,678.79	$43,937,564.80	$15,374,113.99
2016	$62,239,990.72	$47,627,703.84	$14,612,286.88

Recommendations

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

1. Place Vyvanse® (lisdexamfetamine chewable tablets) into Tier-1 based on net cost after rebates.
    a. Current Tier-1 criteria will apply.
    b. A quantity limit of 30 chewable tablets per 30 days will apply.
    c. Vyvanse® capsules and chewable tablets have currently provided a supplemental rebate to be placed in Tier-1; however, Vyvanse® capsules and chewable tablets will be moved to a higher tier based on net cost in comparison to other available products if the manufacturer chooses not to participate in supplemental rebates.
2. Move Aptensio XR™ (methylphenidate ER capsules), generic Metadate CD® (methylphenidate ER capsules), and generic Ritalin LA® (methylphenidate ER capsules) into Tier-1 based on net cost after rebates. Metadate CD® and Ritalin LA® will no longer be brand preferred.
    a. Current Tier-1 criteria will apply.
    b. Aptensio XR™ capsules have currently provided a supplemental rebate to be placed in Tier-1; however, Aptensio XR™ capsules will be moved to a higher tier based on net cost in comparison to other available products if the manufacturer chooses not to participate in supplemental rebates.
3. Move Quillivant XR® (methylphenidate ER suspension) and QuilliChew ER™ (methylphenidate ER chewable tablets) to Tier-2 based on net cost after rebates.
    a. Current Tier-2 criteria will apply.
    b. Quillivant XR® and QuilliChew ER™ will have an age restriction of ten years and younger. Members older than ten years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.
    c. Quillivant XR® suspension and QuilliChew ER™ chewable tablets have currently been placed in Tier-2 based on net cost; however, if the net cost changes, Quillivant XR® suspension and QuilliChew ER™ chewable tablets will be moved to a lower or higher tier based on net cost in comparison to other available products.
4. Move generic Metadate ER® (methylphenidate ER tablets), generic Methylin ER® (methylphenidate ER tablets), and generic Ritalin SR® (methylphenidate ER tablets) into Tier-3 based on net cost after rebates.
    a. Current Tier-3 criteria will apply.
5. Add a previously failed trial of Nuvigil® (armodafinil) for authorization of Provigil® (modafinil), due to a significantly lower net cost of Nuvigil® after rebates.

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

ADHD Medications Tier-2 Approval Criteria:

1. A covered diagnosis; and
2. A previously failed trial with at least one long-acting Tier-1 stimulant that resulted in an inadequate response:

a. Trials should have been within the last 180 days; and
b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician; and

3. For Adzenys XR-ODT™, QuilliChew ER™, and Quillivant XR®, an age restriction of ten years and younger will apply. Members older than ten years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.

ADHD Medications Tier-3 Approval Criteria:

1. A covered diagnosis; and
2. A previously failed trial with at least one long-acting Tier-1 stimulant that resulted in an inadequate response; and
3. A previously failed trial with at least one long-acting Tier-2 stimulant that resulted in an inadequate response:
   a. Trials should have been within the last 365 days; and
   b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.
4. A clinical exception may apply for special formulation products when there is a patient-specific, clinically significant reason why the member cannot use the available long-acting lower tiered formulations.
5. Use of Kapvay® (clonidine extended-release tablets) requires:
   a. An FDA approved diagnosis; and
   b. Previously failed trials (within the last 180 days) with a long-acting Tier-1 stimulant, a long-acting Tier-2 stimulant, Intuniv®, and Strattera®, unless contraindicated, that did not yield adequate results; and
   c. A patient-specific, clinically significant reason why the member cannot use clonidine immediate-release tablets.

ADHD Medications Special Prior Authorization Approval Criteria:

1. Desoxyn®, Dexedrine®, Dexedrine Spansules®, Evekeo®, and Zenzedi® Criteria:
   a. A covered diagnosis; and
   b. A patient-specific, clinically significant reason why the member cannot use all other available stimulant medications.
2. Daytrana®, Dyanavel® XR, ~~QuilliChew ER™, Quillivant XR®,~~ and Methylin® Chewable Tablets and Solution Criteria:
   a. An FDA approved diagnosis; and

b. A patient-specific, clinically significant reason why the member cannot use all other available formulations of long-acting stimulant medications that can be used for members who cannot swallow capsules or tablets; and
c. An age restriction of ten years and younger will apply. Members older than ten years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.

ADHD Medications Additional Criteria:

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

Narcolepsy Medications Approval Criteria:

1. An FDA approved diagnosis; and
2. Use of ~~Provigil® (modafinil) or~~ Nuvigil® (armodafinil) requires a patient-specific, clinically significant reason why the member cannot use stimulant medications to improve wakefulness during the daytime; and
   a. Nuvigil® is <u>brand name preferred</u> due to net cost after rebates; however, brand name preferred status may be removed if the net cost changes and brand name is more costly than generic; and
3. Use of Provigil® (modafinil) requires a previously failed trial (within the last 180 days) with Nuvigil® and a patient-specific, clinically significant reason why the member cannot use stimulant medications to improve wakefulness during the daytime; and
4. Use of Xyrem® (sodium oxybate) requires previously failed trials (within the last 180 days) with Tier-1 and Tier-2 stimulants from different chemical categories, Provigil®, and Nuvigil®, unless contraindicated, that did not yield adequate results; and
5. The diagnosis of obstructive sleep apnea requires concurrent treatment for the obstructive sleep apnea; and
6. The diagnosis of shift work sleep disorder requires the member's work schedule to be included with the prior authorization request.

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

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. **Proposed changes due to supplemental rebate participation are shown in blue. Products may be moved to a higher tier based on net cost if the manufacturer chooses not to participate in supplemental rebates.**

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

ER = extended-release, SR = sustained-release, Caps = capsules, ODT = orally disintegrating tablet, Chew Tabs = chewable tablets, Soln = solution, Susp = suspension

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Appendix J

30-Day Notice to Prior Authorize Radicava™ (Edaravone)

Oklahoma Health Care Authority
July 2017

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

Amyotrophic lateral sclerosis (ALS), commonly referred to as Lou Gehrig's disease, is a rapidly progressive neurodegenerative disease that affects nerve cells (motor neurons) in the brain and spinal cord that control voluntary muscle movement. The progressive degeneration of the motor neurons in ALS eventually leads to their demise. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, people with ALS may lose the ability to speak, eat, move, and breathe. When symptoms begin in the arms or legs, the disease is referred to as "limb onset" ALS, and when speech or swallowing problems are the first symptoms, the disease is referred to as "bulbar onset" ALS. Regardless of the part of the body initially affected by the disease, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10% of people with ALS survive for 10 or more years after the onset of symptoms.

The incidence of ALS is estimated to be 2 per 100,000 people. The prevalence, or number of people living with ALS, varies among geographic regions worldwide; however, it is estimated that approximately 12,000 to 15,000 people in the United States have ALS, with 5,000 new cases being diagnosed every year.[7] ALS affects people of all races and ethnic backgrounds. Symptoms of ALS most commonly develop between the ages of 55 and 75 years, and men are slightly more likely than women to develop ALS. For unknown reasons, military veterans are approximately twice as likely to be diagnosed with ALS than the general public. The majority of ALS cases are considered sporadic, meaning the disease seems to occur at random with no clearly associated risk factors and no family history of the disease. About 5 to 10% of all ALS cases are familial, meaning that an individual inherits the disease from his or her parents. The familial form of ALS usually only requires one parent to carry the gene responsible for the disease, and mutations in over a dozen genes have been found to cause familial ALS.

ALS is a difficult disease to diagnose. There is no single test or procedure to ultimately establish the diagnosis of ALS. It is through a clinical examination and series of diagnostic tests, often ruling out other diseases that mimic ALS, that a diagnosis of ALS can be established. A comprehensive diagnostic workup includes most, if not all, of the following procedures: electrodiagnostic tests including electromyography (EMG) and nerve conduction velocity (NCV); blood and urine studies including high resolution serum protein electrophoresis, thyroid, and parathyroid hormone levels and 24-hour urine collection for heavy metals; spinal tap; x-rays, including magnetic resonance imaging (MRI); myelogram of cervical spine; muscle and/or nerve biopsy; and a thorough neurological examination. These tests are done at the discretion of the physician, usually based on the results of other diagnostic tests and the physical examination.

There are several diseases that have some of the same symptoms of ALS, and most of these conditions are treatable; therefore, the ALS Association recommends that a person diagnosed with ALS seek a second opinion from an ALS expert (someone who diagnoses and treats many ALS patients and has training in this medical specialty).

The El Escorial revised criteria is typically used to help standardize the diagnosis of ALS for clinical research studies. The El Escorial criteria were developed at a conference in El Escorial, Spain in 1994, subsequently revised in a workshop at Airlie House in Warrenton, Virginia in 1998, and again revised in a meeting in Awaji-shima, Japan in 2008; therefore, the names of the criteria, El Escorial revised criteria, Airlie House criteria (or revised criteria), and Awaji-shima criteria, are sometimes used interchangeably. Using this criteria, progressive lower motor neuron disease by clinical and electromyographic examination and clinical upper motor neuron signs are the core, and patients are classified by the number of involved body regions: bulbar, cervical, thoracic, or lumbosacral. The patient's diagnosis is classified as clinically possible ALS, laboratory-supported probable ALS, clinically probable ALS, or clinically definite ALS. It is important to note that the El Escorial and Airlie House diagnostic criteria are excessively restrictive, as some ALS patients are not classified as having definite or probable ALS at the time of their death. The newest Awaji-shima criteria has an increase in sensitivity compared to the original El Escorial criteria that should allow for an earlier diagnosis of ALS and more patients to be recruited to clinical trials at an earlier stage of their disease.

There is currently no cure for ALS; however, there are treatments available that can help control symptoms, prevent unnecessary complications, and make living with the disease easier. Supportive care is best provided by multidisciplinary teams of health care professionals and may include medication, physical therapy, occupational therapy, speech therapy, nutritional support, and respiratory support. Up until just recently, only one medication was approved by the U.S. Food and Drug Administration (FDA) for the treatment of ALS. Rilutek® (riluzole) was FDA approved in 1995 for the treatment of ALS and is believed to reduce damage to motor neurons by decreasing levels of glutamate, which transports messages between nerve cells and motor neurons. Clinical trials in people with ALS showed that riluzole prolongs survival by a few months, particularly in the bulbar form of the disease, but does not reverse the damage already done to motor neurons. Physicians may also prescribe medications to help manage the symptoms of ALS, including muscle cramps, stiffness, excess saliva and phlegm, and pseudobulbar affect.

It is important to note that although the ALS Functional Rating Scale – Revised (ALSFRS-R) is the main outcome measure for ALS studies, a clinically meaningful change in the ALSFRS-R score remains undefined. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0 to 4, with higher scores representing greater functional ability (maximum/best score = 48). ALSFRS-R scores may not be directly comparable from patient to patient since different motor features have different influences on activities of daily living.

Radicava™ (edaravone) was FDA approved in May 2017 as an orphan drug for the treatment of ALS and has been shown to slow the clinical decline in daily functioning of people with ALS. Edaravone was first approved in 2015 in Japan and South Korea for the treatment of ALS, and after learning about the use of edaravone to treat ALS in Japan, the FDA "rapidly engaged with the drug developer about filing a marketing application in the United States".[8] The approval of edaravone in the United States is the first new treatment for ALS approved by the FDA in over 20 years.

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

New FDA Approval(s):

- **May 2017:** The FDA approved Radicava™ (edaravone) for the treatment of ALS.

Other News:

- **August 2016:** Cytokinetics announced that patient enrollment for its VITALITY-ALS clinical trial is complete. The study, designed to assess the effects of tirasemtiv, a novel skeletal muscle activator, on respiratory function in ALS patients, enrolled over 700 people at 81 centers in 11 countries. Tirasemtiv selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium. In preclinical and early clinical studies, it demonstrated increases in skeletal muscle force in response to neuronal input, delays in the onset of muscle fatigue, and reductions in the degree of muscle fatigue. VITALITY-ALS is an international, randomized, double-blind, placebo-controlled trial in patients with possible, probable, or definite ALS. The study's primary endpoint will measure, after 24 weeks, changes from baseline of slow vital capacity (SVC). Secondary endpoints include, among other measures of skeletal muscle strength, time to decline from baseline in percent predicted SVC by ≥ 20 percentage points, or the onset of respiratory insufficiency; time to decline from baseline in percent predicted SVC to ≤ 50 percent predicted, or the onset of respiratory insufficiency; and time to first occurrence of any use of assisted ventilation. Patients will receive two weeks of open-label treatment with tirasemtiv administered at 250mg/day, and will then be randomized to either placebo or to one of three target tirasemtiv dose levels (250mg/day, 375mg/day, or 500mg/day) for 48 weeks. Results from this Phase 3 study are expected in late 2017. Tirasemtiv has been granted orphan drug designation and fast track status by the FDA.
- **December 2016:** Biohaven's BHV-0223 was granted orphan drug designation in the treatment of ALS. BHV-0223 is a sublingually absorbed and orally disintegrating tablet (ODT) formulation of riluzole. BHV-0223's novel formulation is designed to address some of the shortcomings associated with the solid oral dosage formulation of riluzole that ALS patients have difficulty swallowing. Biohaven has completed a pharmacokinetic study with BHV-0223 in humans and is planning to launch a pivotal bioequivalence study in 2017. The FDA approved riluzole oral tablets (brand name Rilutek®) in 1995 for the treatment of ALS, and the recommended dosing is one 50mg tablet taken orally twice daily.
- **May 2017:** AB Science's masitinib showed effectiveness in improving the functioning of patients with ALS. The randomized, double-blind clinical trial compared the efficacy and

safety of combining masitinib with riluzole versus a combination of placebo and riluzole. The study included a total of 394 ALS patients, who were randomly assigned to a treatment combination of masitinib 4.5mg/kg/day and riluzole, masitinib 3mg/kg/day and riluzole, or placebo and riluzole for up to 48 weeks. The results showed that masitinib administered at 4.5mg/kg/day along with riluzole in ALS patients generated a therapeutic benefit when compared to placebo treatment. This masitinib dosage slowed patients' loss of function, improved their progression free survival (PFS), and reduced the decline in quality of life. PFS was defined as either a patient's death or a deterioration of more than nine points in a patient's ALSFRS-R score (*see description in Introduction section*). Masitinib has been granted orphan drug designation by the FDA.

Radicava™ (Edaravone) Product Summary[13,14,15,16,17,18]

FDA Approval: May 2017

Indications: Radicava™ (edaravone) is indicated for the treatment of ALS.

Dosing:

- Radicava™ is supplied for intravenous (IV) infusion in a single-dose polypropylene bag containing 30mg of edaravone in 100mL of clear, colorless aqueous solution.
- The recommended dosage regimen of edaravone is an IV infusion of 60mg administered over a 60-minute period according to the following schedule:
  - An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period
  - Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods
- Edaravone is for IV infusion only. Each 60mg dose of edaravone should be administered as two consecutive 30mg IV infusion bags over a total of 60 minutes (infusion rate approximately 1mg per minute [3.33mL per minute]).
- The IV infusion should be promptly discontinued upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction.
- Other medications should not be injected into the infusion bag or mixed with edaravone.
- Edaravone should be stored in an overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Edaravone should not be used if the oxygen indicator has turned blue or purple before opening the package. Once the overwrap package is opened, edaravone should be used within 24 hours.

Mechanism of Action: The mechanism by which edaravone exerts its therapeutic effect in patients with ALS is unknown. Edaravone is a free radical scavenger that is thought to reduce oxidative stress, a likely factor in the onset and progression of ALS.

Contraindications: Edaravone is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred.

Safety:

- Hypersensitivity Reactions: Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with edaravone. Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, edaravone should be discontinued, and the patient should be treated per standard of care and monitored until the condition resolves.
- Sulfite Allergic Reactions: Edaravone contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.
- Pregnancy: There are no adequate data on the developmental risk associated with the use of edaravone in pregnant women. Based on animal data, edaravone may cause fetal harm. In animal studies, administration of edaravone to pregnant rats and rabbits resulted in adverse developmental effects (increased mortality, decreased growth, delayed sexual development, and altered behavior) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity.
- Lactation: There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Edaravone and its metabolites are excreted in the milk of lactating rats.
- Pediatric Use: The safety and effectiveness of edaravone in pediatric patients have not been established.
- Geriatric Use: Of the 184 patients with ALS who received edaravone in three placebo-controlled clinical trials, a total of 53 patients were 65 years of age and older, including two patients 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
- Renal Impairment: The effect of renal impairment on the pharmacokinetics of edaravone has not been studied. However, renal impairment is not expected to significantly affect the exposure of edaravone. No dosage adjustment is recommended in these patients.
- Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of edaravone has not been studied. No dose adjustment is recommended for patients with mild-to-moderate hepatic impairment. No specific dosing recommendation can be provided for patients with severe hepatic impairment.

Drug Interactions: The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of cytochrome (CYP) enzymes, uridine 5'-diphospho-glucuronosyltransferases (UGTs), or major transporters.

Adverse Reactions: In randomized placebo-controlled ALS clinical trials, the most common adverse reactions (occurred in ≥ 2% of patients in the edaravone-treated group and at least 2% more frequently than in the placebo-treated group) following edaravone treatment were

contusion, gait disturbance, headache, dermatitis, eczema, respiratory failure, respiratory disorder, hypoxia, glycosuria, and tinea infection.

Efficacy: The efficacy of edaravone for the treatment of ALS was established in a six-month, randomized, placebo-controlled, double-blind study **(MCI-186-19)** conducted in Japanese patients with ALS.

- Patients were living independently and met the following criteria at screening:
  - Functionality retained for most activities of daily living (defined as scores of 2 points or better on each individual item of the ALSFRS-R [*see description in Introduction section*])
  - Normal respiratory function (defined as percent-predicted forced vital capacity [%FVC] values of ≥ 80%)
  - Definite or probable ALS based on El Escorial revised criteria
  - Disease duration of 2 years or less
- The study enrolled 69 patients in the edaravone arm and 68 patients in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole.
- Edaravone was administered as an IV infusion of 60mg given over a 60 minute period according to the following schedule:
  - An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
  - Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2 to 6)
- The primary efficacy endpoint was a comparison of change between treatment arms in the ALSFRS-R total scores from baseline to week 24.
- The mean change in ALSFRS-R scores from baseline was -7.50±0.66 for placebo and -5.01±0.64 for edaravone, resulting in a between group difference of 2.49±0.76. The decline in ALSFRS-R scores from baseline was statistically significantly less in the edaravone-treated patients as compared to placebo (p=0.0013). Therefore, edaravone-treated ALS patients meeting the inclusion criteria for the study had less functional loss and less quality of life deterioration at 6 months compared to those receiving standard of care.

Other Clinical Studies:

- A confirmatory double-blind, parallel group, placebo-controlled study **(MCI-186-16)** of efficacy and safety of edaravone was completed in ALS patients:
  - The objective of the study was to confirm the efficacy and safety of edaravone in ALS patients. The study duration was 36 weeks, consisting of a 12-week pre-observation period followed by a 24-week treatment period.
  - Inclusion criteria for the patients were: age 20 to 75 years; diagnosis of “definite”, “probable”, or “probable laboratory-supported” ALS according to the revised Airlie House diagnostic criteria; FVC of at least 70%; duration of disease within three years; and change in ALSFRS-R score during the 12-week pre-observation period of -1 to -4 points. Patients also had a Japanese ALS severity classification of 1 or 2

("1" indicates able to work or perform housework; "2" indicates independent living but unable to work). Administration of riluzole was required not to be changed during the study.
    - Patients were treated with placebo (n=104) or edaravone (n=102), administered as an IV infusion according to the dosing schedule noted previously (*Radicava™ Efficacy section*).
    - The primary efficacy endpoint was the change in the ALSFRS-R scores. Changes in ALSFRS-R scores were -6.35±0.84 in the placebo group and -5.70±0.85 in the edaravone group, with a difference of 0.65±0.78 (p=0.411).
    - The decline in ALSFRS-R scores was smaller in the edaravone group than in the placebo group, but efficacy of edaravone for the treatment of ALS was not demonstrated.
- A long-term safety and efficacy extension study **(MCI-186-17)** of patients diagnosed with ALS and treated with edaravone was completed:
    - The objective of the study was to investigate long-term safety and efficacy of edaravone in a randomized, placebo-controlled, longer-term (7 to 15 months) study following the six-month MCI-186-16 study that failed to confirm efficacy of edaravone in the full analysis population.
    - Patients completing MCI-186-16 study were reassigned to one of three groups: those assigned to edaravone in the preceding study were either randomized to placebo (E-P) or continued on edaravone (E-E); those previously on placebo were assigned to edaravone (P-E).
    - Each treatment cycle included 60mg edaravone or placebo for 10 of 14 days, followed by a 14-day drug-free period. This extension study consisted of cycles 7 to 15.
    - The primary efficacy endpoint was the difference in the ALSFRS-R scores. In the full analysis population, the E-E versus E-P between-group difference in ALSFRS-R for cycles 7 to 12 was 1.16±0.93 (p=0.218). However, analysis of a subgroup with greater baseline functionality (FVC ≥ 80% and with ≥ 2 points for all item scores in the ALSFRS-R at baseline), the difference versus placebo increased to 1.85±1.14 (p=0.113). In further post hoc refinement, requiring definite/probable ALS and study entry ≤ 2 years since first symptom, the difference was further increased to 2.79±1.51 (p=0.072).
    - In conclusion, in patients with greater baseline functionality, longer-term therapy with edaravone may provide a durable and meaningful advantage over placebo.
- A double-blind, parallel group, placebo-controlled exploratory study **(MCI-186-18)** of edaravone for the treatment of advanced ALS was completed:
    - The objective of the study was to explore the possible efficacy of edaravone in ALS patients with more advanced disease, whose impairment excludes independent function. The study duration was 36 weeks, consisting of a 12-week pre-observation period followed by a 24-week treatment period.
    - Inclusion criteria for the patients were: definite, probable, or probable laboratory-supported ALS according to the El Escorial/revised Airlie House diagnostic criteria;

Japan ALS severity classification grade 3 ("3" indicates requiring assistance for eating, excretion, or ambulation); FVC ≥ 60%; duration of disease < 3 years at consent; and change in ALSFRS-R score of -1 to -4 points during the 12-week pre-observation period.

- Patients (n=25) were treated with placebo or edaravone for 6 cycles, administered as an IV infusion according to the dosing schedule noted previously (*Radicava™ Efficacy section*).
- The primary efficacy endpoint was the change in the ALSFRS-R scores from baseline. The mean change in ALSFRS-R score from baseline was -6.52±1.78 in the edaravone group and -6.00±1.83 in the placebo group. The mean between-group difference (placebo-edaravone) change from baseline through cycle 6 was -0.52±2.46 (p=0.835).
- In conclusion, no difference between edaravone and placebo treatment was discerned in this exploratory study in patients with more advanced ALS.

Cost: Radicava™ is expected to be available in the United States in August 2017; however, cost information for Radicava™ is not currently available.

Recommendations

The College of Pharmacy recommends the prior authorization of Radicava™ (edaravone) with the following criteria:

Radicava™ (Edaravone) Approval Criteria:

1. An FDA approved diagnosis of amyotrophic lateral sclerosis (ALS); and
2. Member must have been evaluated by a physician specializing in the treatment of ALS within the last three months; and
3. Disease duration of two years or less (for initial approval); and
    a. A prior authorization request with patient-specific information may be submitted for consideration of edaravone for members with disease duration greater than two years, including but not limited to disease progression, specific symptoms related to the disease, activities of daily living currently affected by the disease, or prognosis; and
4. Approvals will be for the duration of six months. For each subsequent approval, the prescriber must document that the member is responding to the medication, as indicated by a slower progression in symptoms and/or decline in quality of life compared to the typical ALS disease progression.

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Appendix K

Calendar Year 2016 Annual Review of Atopic Dermatitis (AD) Medications and 30-Day Notice to Prior Authorize Eucrisa™ (Crisaborole 2% Ointment), Dupixent® (Dupilumab Injection), & Prudoxin™ and Zonalon® (Doxepin 5% Cream)

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Elidel® (Pimecrolimus Topical) and Protopic® (Tacrolimus Topical) Approval Criteria:

1. The first 90 days of a 12 month period will be covered without prior authorization.
2. After the initial period, authorization may be granted with documentation of one trial at least six weeks in duration within the past 90 days of a Tier-1 topical corticosteroid.
3. Therapy will be approved only once each 90 day period to ensure appropriate short-term and intermittent utilization as advised by the U.S. Food and Drug Administration (FDA).
4. Quantities will be limited to 30 grams for use on the face, neck, and groin, and 100 grams for all other areas.
5. Authorizations will be restricted to those patients who are not immunocompromised.

Members Must Meet All of the Following Criteria for Authorization:

1. An FDA approved diagnosis:
    a. Elidel®: short-term and intermittent treatment for mild-to-moderate atopic dermatitis (eczema)
    b. Protopic®: short-term and intermittent treatment for moderate-to-severe atopic dermatitis (eczema)
2. Age Restrictions:
    a. Elidel® 1% is restricted to two years of age and older
    b. Protopic® 0.03% is restricted to two years of age and older
    c. Protopic® 0.1% is restricted to 15 years of age and older

Clinical Exceptions for Children Meeting Age Restriction:

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

Clinical Exceptions for Children <u>Not</u> Meeting Age Restriction: Prescribed by dermatologist.

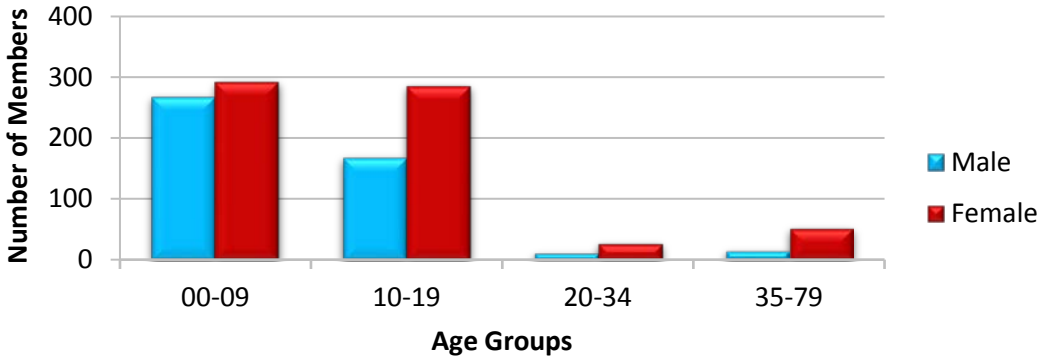
Utilization of AD Medications: Calendar Year 2016

Comparison of Calendar Years

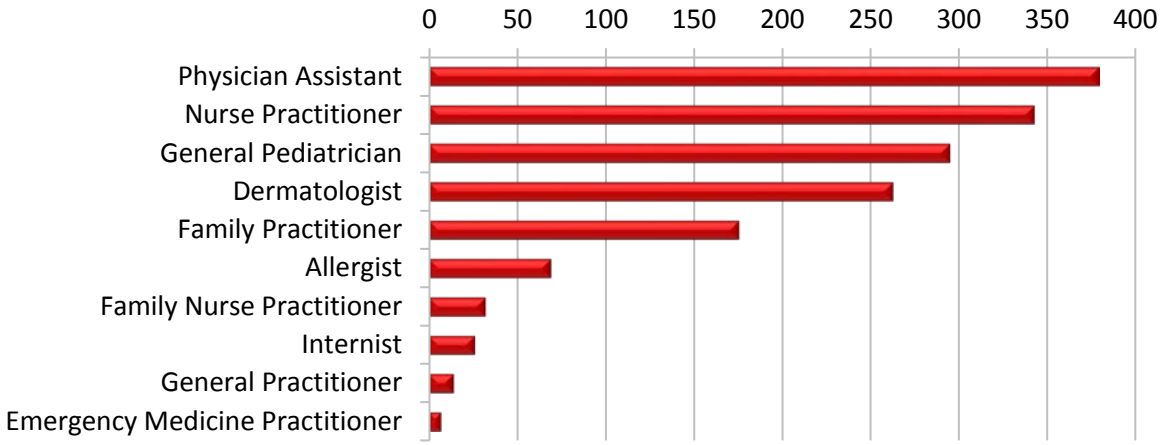
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	1,227	1,733	$554,535.88	$319.99	$10.17	82,440	54,512
2016	1,118	1,620	$512,562.38	$316.40	$9.97	80,090	51,415
% Change	**-8.90%**	**-6.50%**	**-7.60%**	**-1.10%**	**-2.00%**	**-2.90%**	**-5.70%**
Change	**-109**	**-113**	**-$41,973.50**	**-$3.59**	**-$0.20**	**-2,350**	**-3,097**

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

Demographics of Members Utilizing AD Medications



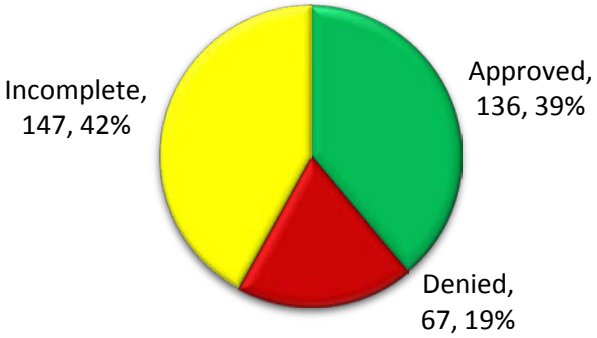
Top Prescriber Specialties of AD Medications by Number of Claims



Prior Authorization of AD Medications

There were 350 prior authorization requests submitted for AD medications during calendar year 2016. 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]

Anticipated Patent Expiration(s):

- Elidel® (pimecrolimus): December 2018

New FDA Approval(s):

- **December 2016:** The U.S. Food and Drug Administration (FDA) approved Eucrisa™ (crisaborole ointment) for the treatment of mild-to-moderate eczema (AD) in patients two years of age and older.
- **March 2017:** The FDA approved Dupixent® (dupilumab injection) for the treatment of adults with moderate-to-severe eczema (AD). Dupilumab is intended for patients whose eczema is not adequately controlled with topical therapies or for those patients for whom topical therapies are not advisable.

Pipeline:

- **Lebrikizumab:** Results of a Phase 2 study of lebrikizumab, a humanized monoclonal antibody that binds to soluble interleukin-13 (IL-13) with high affinity, in the treatment of moderate-to-severe AD were presented at the annual congress of the European Academy of Dermatology and Venereology in 2016. The trial, TREBLE, was a double-blind, dose-ranging study involving 209 adults with moderate-to-severe AD despite intensive topical corticosteroid (TCS) therapy. The primary endpoint was the percentage of patients who achieved at least a 50% reduction from baseline on the Eczema Area and Severity Index (EASI), or EASI 50. The EASI 50 rate was 62.3% in patients on placebo plus daily TCS, 69.2% with a single 125mg dose of lebrikizumab, 69.8% with a single 250mg dose of lebrikizumab, and 82.4% with 125mg of lebrikizumab at weeks 0, 4, 8, and 12. Only the group with monthly dosing of lebrikizumab plus daily triamcinolone 0.1% twice daily had an EASI 50 response rate significantly better than placebo plus TCS.
- **Nemolizumab:** Results of a small, 3-month Phase 2 trial of monthly subcutaneous (sub-Q) injections of nemolizumab, a humanized monoclonal antibody that inhibits IL-31 signaling, were published online in March 2017 in the *New England Journal of Medicine*. Nemolizumab significantly improved pruritus associated with AD. The study involved 264 adults with refractory moderate-to-severe AD, inadequately controlled with topical treatments. The primary efficacy endpoint was the percentage improvement in scores on a pruritus visual analogue scale at week 12. These scores improved significantly in a

dose-dependent manner for nemolizumab treatment, compared with placebo. Pruritus declined by 43.7% with the 0.1mg/kg dose (p=0.002), 59.8% with the 0.5mg/kg dose (p<0.001), and 63.1% with the 2mg/kg dose (p<0.001), compared with 20.9% for placebo.

- **Tralokinumab:** Leo Pharma announced positive results from a Phase 2b dose-ranging efficacy and safety study of tralokinumab, an investigational monoclonal antibody that targets cytokine IL-13, in adult patients with moderate-to-severe AD. The study included 204 adults with moderate-to-severe AD despite a two week run-in with continuous mid-strength TCS treatment. The co-primary endpoints were change from baseline in EASI and percentage of patients with clear or almost clear Investigator's Global Assessment (IGA 0/1) at week 12. Following treatment with tralokinumab for 12 weeks, tralokinumab 150mg and 300mg significantly reduced total EASI from baseline (adjusted mean difference of -4.4, p=0.027 and -4.9, p=0.011, respectively) compared with placebo. At week 12, the number of patients achieving EASI 50 in the tralokinumab 300mg group was significantly higher compared with placebo (73.4% vs. 51.9%, p=0.025).
- **Ustekinumab:** Stelara® (ustekinumab) is a long-acting injectable human IL-12 and IL-23 antagonist currently FDA approved for moderate-to-severe plaque psoriasis and active psoriatic arthritis. Results of a Phase 2 study of adults with moderate-to-severe AD treated with ustekinumab were presented at the 2016 annual meeting of the Society for Investigative Dermatology. The proportion of responders (patients with at least a 50% decline from baseline score on the Scoring Atopic Dermatitis severity scale) was greater for ustekinumab than placebo at weeks 12, 16, 20; however, the differences never reached statistical significance.

Other News:

- **June 2017:** The Institute of Clinical and Economic Review (ICER) issued a Final Evidence Report that concludes that Dupixent® (dupilumab) resulted in substantial improvements in AD in the majority of patients that were studied. The report also noted that treatment with dupilumab improved quality of life in addition to improving the severity of AD and reducing pruritus. The report also assesses the comparative clinical effectiveness of Eucrisa™ (crisaborole) for mild-to-moderate disease. The review found inadequate evidence to assess the relative efficacy of crisaborole compared with the other topical therapies for AD, although the efficacy of crisaborole appears likely to be less than that of topical tacrolimus and higher potency TCS.

Eucrisa™ (Crisaborole 2% Ointment) Product Summary[10]

Indication(s): Eucrisa™ (crisaborole) is a phosphodiesterase 4 (PDE-4) inhibitor indicated for topical treatment of mild-to-moderate AD in patients 2 years of age and older.

Dosing:

- Eucrisa™ 2% ointment is supplied in 60g and 100g laminate tubes.
- It is recommended to apply a thin layer of crisaborole twice daily to the affected areas. Crisaborole is for topical use only and is not for ophthalmic, oral, or intravaginal use.

Mechanism of Action: Crisaborole is a PDE-4 inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of AD is not well defined.

Contraindications:

- Patients with known hypersensitivity to crisaborole or any component of the formulation.

Warnings and Precautions:

- Hypersensitivity Reactions: Crisaborole should be discontinued immediately and appropriate therapy initiated if signs and symptoms of hypersensitivity occur.

Adverse Reactions: The most common adverse reaction to crisaborole occurring in at least 1% of subjects was application site pain.

Use in Specific Populations:

- Pregnancy: There is no available data with crisaborole in pregnant women to inform the drug-associated risk for miscarriage and major birth defects. There were no adverse developmental effects observed in animal reproduction studies with oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to five and thre times, respectively, the maximum recommended human dose (MRHD).
- Lactation: There is no available data on the presence of crisaborole in human milk, the effects of the drug on breastfed infants, or the effects of the drug on milk production after topical application of crisaborole to women who are breastfeeding. Crisaborole is systemically absorbed.
- Pediatric Use: The safety and effectiveness of crisaborole have been established in pediatric patients 2 years of age and older for topical treatment of mild-to-moderate AD. The safety and effectiveness of the medication in patients below the age of 2 years have not been established.
- Geriatric Use: Clinical studies of crisaborole did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently to the medication than younger subjects.

Efficacy:

- The efficacy of crisaborole was evaluated in two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials. A total of 1,522 subjects 2 to 79 years of age with a 5% to 95% treatable body surface area (BSA) were included. At baseline, 38.5% of the subjects had an Investigator's Static Global Assessment (ISGA) score of 2 (mild), and 61.5% had an ISGA score of 3 (moderate) in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to 4.
- In both trials, subjects were randomized 2:1 to receive crisaborole or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 who achieved success, defined as an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline, comparing crisaborole-treated subjects to vehicle-treated subjects.

- In Trial 1, 32.8% (n=503) of crisaborole-treated subjects achieved success in ISGA compared to 25.4% (n=256) of vehicle-treated subjects. In Trial 2, 31.4% (n=513) of crisaborole-treated subjects versus 18.0% (n=250) of vehicle-treated subjects achieved success in ISGA.

Dupixent® (Dupilumab Injection) Product Summary[11]

Indication(s): Dupixent® (dupilumab injection) is an IL-4 alpha antagonist indicated for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without TCS.

Dosing:

- Dupixent® is supplied in single-dose pre-filled syringes. Each pre-filled syringe is designed to deliver 300mg of dupilumab in 2mL solution. Dupilumab is available in cartons containing two pre-filled syringes.
- Dupilumab should be stored in the refrigerator at 36°F to 46°F. If necessary, pre-filled syringes may be kept at room temperature up to 77°F for a maximum of 14 days. After removal from the refrigerator, dupilumab must be used within 14 days or discarded.
- The recommended dose is an initial dose of 600mg (two 300mg injections in different injection sites), followed by 300mg given every other week. Dupilumab is administered by sub-Q injection.

Mechanism of Action: Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE.

Contraindications:

- Patients with known hypersensitivity to dupilumab or any of its excipients.

Warnings and Precautions:

- Hypersensitivity: Hypersensitivity reactions, including generalized urticaria and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received dupilumab in clinical trials. Two subjects experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. If a clinically significant hypersensitivity reaction occurs, appropriate therapy should be instituted and dupilumab should be discontinued.
- Conjunctivitis and Keratitis: Conjunctivitis and keratitis occurred more frequently in subjects who received dupilumab. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in less than 1% of subjects in the dupilumab treatment group and in 0% of subjects in the placebo group in the 16-week monotherapy trials. In the 52-week dupilumab plus TCS trial, keratitis was reported in

4% of the dupilumab plus TCS group and in 0% of the placebo plus TCS group. Most subjects with keratitis recovered or were recovering during the treatment period. Patients should be advised to report new onset or worsening eye symptoms to their healthcare provider.

- Comorbid Asthma: Dupilumab safety and efficacy have not been established in the treatment of asthma. Patients with comorbid asthma should be advised not to adjust or stop their asthma treatments without consultation with their physicians.
- Parasitic (Helminth) Infections: Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if dupilumab will influence the immune response against helminth infections.

Adverse Reactions: The most common adverse reactions to dupilumab (incidence greater than or equal to 1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, and dry eye.

Use in Specific Populations:

- Pregnancy: There are no available data with dupilumab in pregnant women to inform any drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, dupilumab may be transmitted to the developing fetus from the mother. No adverse developmental effects were observed in offspring born to pregnant monkeys in an enhanced pre- and post-natal developmental study after sub-Q administration of a homologous antibody against IL-4Rα during organogenesis through parturition at doses up to 10-times the MRHD.
- Lactation: There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown.
- Pediatric Use: The safety and effectiveness of dupilumab in pediatric patients under 18 years of age have not been established.
- Geriatric Use: Of the 1,472 subjects with AD exposed to dupilumab in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years of age or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects 65 years and older is not sufficient to determine whether they respond differently from younger subjects.

Efficacy:

- The efficacy of dupilumab was evaluated in three randomized, double-blind, placebo-controlled trials. A total of 2,119 subjects 18 years of age and older with moderate-to-severe AD not adequately controlled by topical medication(s) were enrolled. The disease severity was defined by an IGA score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an EASI score ≥ 16 on a scale of 0 to 72, and a minimum BSA involvement of ≥ 10%. At baseline, 52% of subjects had a baseline IGA score of 3 (moderate AD) and 48% of subjects had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0 to 10.

- In all three trials, subjects in the dupilumab group received 600mg of dupilumab administered via sub-Q injection at Week 0, followed by 300mg every other week (Q2W). In the monotherapy trials, subjects received dupilumab or placebo for 16 weeks. In the concomitant therapy trial, subjects received dupilumab or placebo with concomitant TCS and as needed topical calcineurin inhibitors for problem areas only (e.g., face, neck, intertriginous, and genital areas) for 52 weeks.
- In all three trials the primary endpoint was the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the peak pruritus NRS from baseline at Week 16.
- In the first monotherapy trial, 38% of subjects receiving dupilumab Q2W achieved an IGA score of 0 or 1 and reduction of ≥ 2 points from baseline at week 16 versus 10% for placebo ($p<0.001$).
- In the second monotherapy trial, 36% of subjects receiving dupilumab Q2W achieved an IGA score of 0 or 1 and reduction of ≥ 2 points from baseline at week 16 versus 9% for placebo ($p<0.001$).
- In the concomitant therapy trial, 39% of subjects receiving dupilumab Q2W plus TCS achieved an IGA score of 0 or 1 and reduction of ≥ 2 points from baseline at week 16 versus 12% for placebo ($p<0.001$).

Prudoxin™ and Zonalon® (Doxepin 5% Cream) Product Summary[12,13,14]

Indications: Doxepin cream is indicated for the short-term (up to 8 days) management of moderate pruritus in adult patients with AD or lichen simplex chronicus.

Dosing:

- It is recommended to apply a thin film of cream four times each day with at least a 3 to 4 hour intervals between applications.
- There are no data to establish the safety and effectiveness of doxepin cream when used for greater than 8 days. Chronic use beyond 8 days may result in higher systemic levels and should be avoided. Use of doxepin cream for longer than 8 days may result in an increased likelihood of contact sensitization.
- Greater body surface application of doxepin cream may increase the risk for sedation. Clinical experience has shown that drowsiness is significantly more common in patients applying doxepin cream to over 10% of their BSA. Patients with greater than 10% of BSA affected should be particularly cautioned concerning possible drowsiness and other systemic adverse effects of doxepin. If excessive drowsiness occurs, it may be necessary to do one or more of the following: reduce the number of applications per day, reduce the amount of cream applied, reduce the BSA treated, or discontinue the drug.
- It is recommended not to utilize occlusive dressings with doxepin cream as they may increase the absorption of topical drugs.

Mechanism of Action: Doxepin has H_1 and H_2 histamine receptor blocking actions, however the exact mechanism by which doxepin exerts its antipruritic effect is unknown.

Contraindications:

- Patients with untreated narrow angle glaucoma or a tendency towards urinary retention because doxepin has an anticholinergic effect and significant plasma levels of doxepin are detectable after topical application
- Patients with previous sensitivity to doxepin or any of the components of the formulation

Warnings and Precautions:

- Drowsiness: Drowsiness occurs in over 20% of patients treated with doxepin cream, especially in patients receiving treatment to greater than 10% of their BSA. Patients should be warned about the possibility of sedation and cautioned to avoid driving a motor vehicle or operating hazardous machinery while being treated with doxepin cream. When doxepin cream is used, the sedating effects of alcoholic beverages, antihistamines, and other CNS depressants may be potentiated. Sedating drugs may cause confusion and oversedation in the elderly. Elderly patients should be observed closely for confusion and oversedation when started on doxepin cream.
- Use Under Occlusion: Occlusive dressings should not be utilized with doxepin cream as occlusive dressings may increase the absorption of most topical drugs.
- Contact Sensitization: Use of doxepin cream may cause Type IV hypersensitivity reactions (contact sensitization) to doxepin.

Adverse Reactions: In controlled clinical trials of patients treated with doxepin cream, the most common systemic adverse event reported was drowsiness. The most common local site adverse reaction reported during controlled clinical trials of patients treated with doxepin cream was burning and/or stinging at the site of application.

Use in Specific Populations:

- Pregnancy: Doxepin is Pregnancy Category B. Reproduction studies have been performed in which doxepin was administered orally to rats and rabbits at doses up to 0.6 and 1.2 times, respectively, the estimated exposure to doxepin that results from use of 16 grams of topical doxepin cream per day. The studies have revealed no evidence of harm to rat or rabbit fetuses due to doxepin. However, there are no adequate and well-controlled studies in pregnant women.
- Nursing Mothers: Following oral administration, doxepin is excreted in human milk. It is possible that doxepin may also be excreted in human milk following topical application. One case has been reported of apnea and drowsiness in a nursing infant whose mother was taking an oral dosage form of doxepin.
- Pediatric Use: The use of doxepin cream in pediatric patients is not recommended. Safe conditions for the use of doxepin cream in children have not been established. One case has been reported of a 2.5 year old child who developed somnolence, grand mal seizure, respiratory depression, ECG abnormalities, and coma after treatment with doxepin cream.

- Geriatric Use: Clinical studies of doxepin cream did not include sufficient numbers of subjects 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Efficacy:

- A total of 270 patients with AD who had daily moderate-to-severe pruritus for at least 1 week were enrolled in a double-blind, vehicle-controlled, multi-center study. Treatment was randomly assigned to doxepin 5% cream or vehicle cream applied twice on the day of the baseline visit and four times daily with 3 to 4 hour intervals in between applications for the remainder of the 7-day trial. In the doxepin treated group, 85% of patients achieved significant relief of pruritus symptoms by day 7 versus 57% of patients in the vehicle group ($p<0.01$). A majority of positive responses occurred within the first 24 hours.

Cost Comparison: Medications for AD

Medication	Recommended Dosing Regimen	Cost/Unit	Cost/Month
Dupixent® (dupilumab)	**300mg subQ Q2W**	**$1,423.08**	**$2,846.16**
Eucrisa™ (crisaborole), 60gm	**Apply twice daily**	**$561.60**	**$561.60**
doxepin cream, 45gm	**Apply 4 times daily**	**$479.70**	**$479.70**
alclometasone dipropionate 0.05%, 60gm	Apply 2 to 3 times daily	$71.40	$71.40
betamethasone valerate 0.1% oint, 45gm	Apply 1 to 3 times daily	$25.65	$25.65
augmented betamethasone dipropionate 0.05% gel, 50gm	Apply 1 to 2 times daily	$104.00	$104.00
Elidel® (pimecrolimus 1%), 60gm	Apply twice daily	$492.60*	$492.60*
Protopic® (tacrolimus 0.03%), 60gm	Apply twice daily	$340.80*	$340.80*
Protopic® (tacrolimus 0.1%), 60gm	Apply twice daily	$343.20*	$343.20*

SubQ = subcutaneous; gm = gram; oint = ointment; Q2W = every other week
Cost based on National Average Drug Acquisition Cost (NADAC), State Maximum Allowable Cost (SMAC), or Wholesale Acquisition Cost (WAC) if NADAC unavailable. Costs listed in the table above do not take into account federal or supplemental rebate participation; therefore, do not reflect net costs.
*Protopic® was FDA approved in 2000 and Elidel® was FDA approved in 2001; both have significant rebates

Recommendations

The College of Pharmacy recommends the prior authorization of Eucrisa™ (crisaborole), Dupixent® (dupilumab), and Prudoxin™ and Zonalon® (doxepin cream) with the following criteria:

Eucrisa™ (Crisaborole Ointment) Approval Criteria:

1. An FDA approved indication for treatment of mild-to-moderate atopic dermatitis (eczema); and
2. Member must be at least 2 years of age or older; and

3. Member must have documented trials within the last six months for a minimum of two weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. One Tier-1 topical corticosteroid; and
    b. One topical calcineurin inhibitor [e.g., Elidel® (pimecrolimus), Protopic® (tacrolimus)]; and
4. A quantity limit of one tube per 30 days will apply.
5. Initial approvals will be for the duration of one month. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Dupixent® (Dupilumab Injection) Approval Criteria:

1. An FDA approved diagnosis of moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies; and
2. Member must be 18 years of age or older; and
3. Member must have documented trials within the last six months for a minimum of two weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. One medium potency to very-high potency Tier-1 topical corticosteroid; and
    b. One topical calcineurin inhibitor [e.g., Elidel® (pimecrolimus), Protopic® (tacrolimus)]; and
4. Dupixent® must be prescribed by a dermatologist, allergist, or immunologist or the member must have been evaluated by a dermatologist, allergist, or immunologist within the last twelve months (or an advanced care practitioner with a supervising physician who is a dermatologist, allergist, or immunologist); and
5. Initial approvals will be for the duration of 16 weeks. Reauthorization may be granted if the prescriber documents the member is responding well to treatment. Additionally, compliance will be evaluated for continued approval.

Prudoxin™ and Zonalon® (Doxepin Cream) Approval Criteria:

1. An FDA approved diagnosis for the short-term (up to eight days) management of moderate pruritus in patients with atopic dermatitis or lichen simplex chronicus; and
2. Requests for longer use than eight days will not generally be approved. Chronic use beyond eight days may result in higher systemic levels and should be avoided.

Utilization Details of AD Medications: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
TACROLIMUS OIN 0.03%	798	554	$237,575.19	$9.73	$297.71	46.35%
ELIDEL CRE 1%	666	473	$229,654.07	$10.23	$344.83	44.81%
TACROLIMUS OIN 0.1%	137	100	$35,534.74	$8.64	$259.38	6.93%
DOXEPIN HCL CRE 5%	14	11	$7,966.11	$23.02	$569.01	1.55%
PRUDOXIN CRE 5%	4	4	$1,339.72	$20.00	$334.93	0.26%
PROTOPIC OIN 0.03%	1	1	$492.55	$16.42	$492.55	0.10%
TOTAL	**1,620**	**1,118***	**$512,562.38**	**$9.97**	**$316.40**	**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 Vimizim® (Elosulfase Alfa)

Oklahoma Health Care Authority
July 2017

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

Morquio syndrome, also known as mucopolysaccharidosis type IV or MPS IV, is a progressive condition that is characterized by skeletal involvement, but is also associated with significant non-skeletal manifestations including respiratory disease, spinal cord compression, cardiac disease, impaired vision, hearing loss, and dental problems. Morquio syndrome is inherited in an autosomal recessive pattern and there are two forms with similar clinical findings. Morquio A (MPS IVA) results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS) and Morquio B (MPS IVB) results from a deficiency of beta-galactosidase. The clinical features of the syndrome result from accumulation of chondroitin-6-sulfate and keratin sulfate.

Morquio A's phenotypic spectrum is a continuum and ranges from a severe and rapidly progressive early-onset form to a slowly progressive later-onset form. At birth, children with Morquio A syndrome do not have any distinctive clinical findings. The most severe form typically becomes apparent between the age of 1 and 3 years; however, the slowly progressive form may not become evident until late childhood or adolescence. Affected individuals develop various skeletal abnormalities, such as pectus carinatum (protuberant sternum), genu valgum (knock-knee deformity), and kyphoscoliosis. Progressive bone and joint involvement eventually leads to disabling pain and arthritis. By the second or third decade of life, patients may be confined to wheelchairs. In the severe forms of the disease, death usually occurs in the third or fourth decade of life due to cardiorespiratory failure. Patients with a more mild form may survive into the seventh decade.

The exact prevalence of Morquio syndrome is unknown; however, it is estimated to occur in 1 in 200,000 to 300,000 individuals. Females and males are equally affected. Morquio A occurs more frequently than Morquio B. The diagnosis of Morquio A syndrome is done by analysis of *N*-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity or by molecular genetic testing with identification of biallelic pathogenic variants in *GALNS.*

The U.S. Food and Drug Administration (FDA) approved Vimizim® (elosulfase alfa), an enzyme replacement therapy with recombinant human GALNS, in 2014 for the treatment of Morquio A syndrome. Prior to the approval of elosulfase alfa, treatment of Morquio A syndrome was limited to supportive, symptomatic care. Physical therapy, surgery, symptom-based medications, and rehabilitation may be used in the treatment of patients with Morquio A syndrome.

Vimizim® (Elosulfase Alfa) Product Summary[8]

FDA Approval: 2014

Indications: Vimizim® (elosulfase alfa) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Morquio A syndrome (Mucopolysaccharidosis type IVA, MPS IVA).

Dosing:

- Vimizim® is available as a concentrated solution for infusion (1mg per mL) requiring dilution; one vial of 5mL contains 5mg elosulfase alfa. The vials are for single-use only and any unused product should be discarded.
- The recommended dosage regimen of elosulfase alfa is 2mg per kilogram (kg) of body weight administered once weekly as an intravenous (IV) infusion over a minimum of 3.5 to 4.5 hours, based on infusion volume.
- Pre-treatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of the infusion.
- Elosulfase alfa does not contain preservatives; therefore, the product should be used immediately after dilution. If immediate use is not possible, the diluted solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours followed by up to 24 hours at 23°C to 27°C (73°F to 81°F). Administration of elosulfase alfa should be completed within 48 hours from the time of dilution.

Boxed Warning: Risk of Anaphylaxis

- Life-threatening anaphylactic reactions have occurred in some patients during elosulfase alfa infusions. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, and gastrointestinal symptoms in conjunction with urticaria, have been reported during elosulfase alfa infusions, regardless of the duration of the course of treatment. Patients should be closely observed during and after elosulfase alfa administration and healthcare professionals should be prepared to manage anaphylaxis. Patients should be informed of the signs and symptoms of anaphylaxis and should be instructed to seek immediate medical care should these symptoms occur. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring.

Mechanism of Action: MPS comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of GAG. MPS IVA is characterized by the absence or marked reduction in *N*-aceytlgalactosamine-6-sulfatase activity. The sulfatase activity deficiency results in the accumulation of the GAG substrates, keratin sulfate (KS) and chondroitin-6-sulfate (C6S), in the lysosomal compartment of cells. The accumulation of GAG substrates leads to widespread cellular, tissue, and organ dysfunction. Elosulfase alfa is intended to provide the exogenous enzyme *N*-aceytlgalactosamine-6-sulfatase that will be taken up into the lysosomes and increase catabolism of KS and C6S. Elosulfase alfa

uptake by cells into lysosomes is mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to mannose-6-phosphate receptors.

Contraindications: None.

Warnings and Precautions:

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been reported in some patients treated with elosulfase alfa. Due to the potential for anaphylaxis, appropriate medical support should be readily available when elosulfase alfa is administered. Patients should be closely observed for an appropriate amount of time after administration, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials. Patients should be informed of the signs and symptoms of anaphylaxis and should be instructed to seek immediate medical care should signs and symptoms occur. It is recommended to administer antihistamines with or without antipyretics prior to infusion due to the potential for hypersensitivity reactions. The management of hypersensitivity reactions depends on the severity of the reaction and may include slowing or temporarily interrupting the infusion and/or administering additional antihistamines, antipyretics, and/or corticosteroids for mild reactions. If severe hypersensitivity reactions occur, the elosulfase alfa infusion should be immediately stopped and appropriate treatment should be initiated. The risks and benefits of re-administering elosulfase alfa should be considered following a severe reaction.
- Risk of Acute Respiratory Complications: Patients with acute febrile or respiratory illness at the time of elosulfase alfa infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Prior to administration of elosulfase alfa, careful consideration should be given to the patient's clinical status and the elosulfase alfa infusion may need to be delayed. In patients with MPS IVA, sleep apnea is common. Prior to initiation of treatment with elosulfase alfa, an evaluation of airway patency should be considered. It is recommended that patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an acute reaction, or extreme drowsiness induced by antihistamine use.
- Spinal or Cervical Cord Compression: A known and serious complication of MPS IVA is spinal or cervical cord compression (SCC) and may occur as part of the natural history of the disease. In clinical trials, SCC was observed in both patients receiving elosulfase alfa and in patients receiving placebo. It is recommended that patients with MPS IVA be monitored for signs and symptoms of SCC (e.g., back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence) and appropriate clinical care should be given.

Adverse Reactions: In clinical trials, the most common adverse reactions (≥10% in elosulfase alfa-treated patients and occurring at a higher incidence than placebo-treated patients) were pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue.

Use in Specific Populations:

- Pregnancy: Pregnancy Category B. There is a Morquio A Registry that collects data on pregnant women with MPS IVA who are treated with elosulfase alfa. There are no adequate and well-controlled studies with elosulfase alfa in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed in rats given daily administration of elosulfase alfa up to 33 times the human steady-state area under the curve (AUC) at the recommended human weekly dose pre-mating and through the period of organogenesis. No effects on embryo-fetal development were observed in rabbits given daily administration of elosulfase alfa at doses up to 8 times the human steady-state AUC at the recommended weekly dose during organogenesis, which produced maternal toxicity. A dose-dependent increase in stillbirths was observed when elosulfase alfa was administered daily in rats during organogenesis through lactation at doses 5 times the human steady-state AUC at the recommended human weekly dose. An increase in pup mortality was observed at doses producing maternal toxicity. Elosulfase alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: It is not known whether elosulfase alfa is present in human milk. Elosulfase alfa was present in milk from treated rats.
- Pediatric Use: The safety and effectiveness of elosulfase alfa in pediatric patients 5 years of age and older have been established. Adequate and well-controlled trials in pediatric and adult patients support use of elosulfase alfa in patients 5 years of age and older. Clinical trials with elosulfase alfa were conducted in 176 patients (median age 12 years, range 5 to 57 years) with the majority of patients in the pediatric age group. The safety and effectiveness in pediatric patients younger than 5 years of age have not been established.
- Geriatric Use: Clinical studies of elosulfase alfa did not include any patients 65 years of age or older. It is not known whether they respond differently than younger patients.

Efficacy: The safety and efficacy of elosulfase alfa were evaluated in a 24-week, randomized, double-blind, placebo-controlled clinical trial of 176 patients with MPS IVA.

- The majority of the patients (82%) presented with a medical history of musculoskeletal conditions, which included knee deformity (52%), kyphosis (31%), hip dysplasia (22%), prior spinal fusion surgery (22%), and arthralgia (20%). The age of the patients ranged from 5 to 57 years.
- Patients received elosulfase alfa 2mg/kg once per week (n=58), elosulfase alfa 2mg/kg once every other week (n=59), or placebo (n=59).
- The primary efficacy endpoint was the change from baseline in the distance walked in six minutes (six minute walk test, 6-MWT) at Week 24. The treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5m (CI_{95}, 4.0, 40.9; p=0.0174) in patients who received elosulfase alfa 2mg/kg once per week. Patients who received elosulfase alfa 2mg/kg once every other week performed similarly in the 6-MWT as those who received placebo.
- The other endpoints included changes from baseline in the rate of stair climbing in three minutes (three-minute stair climb test, 3-MSCT) and changes from baseline in urine KS

levels at Week 24. There was no difference in the rate of stair climbing between patients who received elosulfase alfa and those who received placebo. The reduction in urinary KS levels from baseline, a measure of pharmacodynamic effect, was greater in the elosulfase alfa treatment groups compared to placebo. The relationship between urinary KS and other measures of clinical response has not been established.

- Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. One hundred seventy-three of 176 patients enrolled in the extension trial. Patients received either elosulfase alfa 2mg/kg once per week (n=86) or elosulfase alfa 2mg/kg once every other week (n=87). In patients who continued to receive elosulfase alfa 2mg/kg once per week for another 48 weeks, walking ability showed no further improvement beyond the first 24 weeks of treatment in the placebo-controlled trial.

Utilization: There was no utilization of Vimizim® (elosulfase alfa) during calendar year 2016.

Cost: The wholesale acquisition cost (WAC) of Vimizim® (elosulfase alfa) is $1,111.00 per 5mg/5mL single-use vial for IV use.

Patient Weight	Dosing Regimen	Vials Per Infusion	Cost Per Weekly Infusion	Cost Per Year
10kg	20mg once weekly	4	$4,444.00	$231,088.00
20kg	10mg once weekly	8	$8,888.00	$462,176.00
55kg	110mg once weekly	22	$24,442.00	$1,270,984.00

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

Recommendations

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

Vimizim® (Elosulfase Alfa) Approval Criteria:

1. An FDA approved diagnosis of Morquio A syndrome (mucopolysaccharidosis type IVA; MPS IVA) confirmed by:
    a. Enzyme assay demonstrating a deficiency of N-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity; or
    b. Molecular genetic testing to confirm biallelic pathogenic variants in *GALNS*; and
2. Vimizim® must be administered by a healthcare professional prepared to manage anaphylaxis; and
3. Initial approvals will be for the duration of twelve months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.
4. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

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Appendix M

Calendar Year 2016 Annual Review of Natpara® (Parathyroid Hormone Injection) and 30-Day Notice to Prior Authorize Rayaldee® (Calcifediol), Parsabiv™ (Etelcalcetide), Zemplar® (Paricalcitol Capsules), and Hectorol® (Doxercalciferol Capsules)

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Natpara® (Parathyroid Hormone) Approval Criteria:

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

Utilization of Parathyroid Medications: Calendar Year 2016

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

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	1	8	$66,882.96	$8,360.37	$298.58	16	224
2016	1	13	$113,690.80	$8,745.45	$312.34	26	364
% Change	**0.00%**	**62.50%**	**70.00%**	**4.60%**	**4.60%**	**62.50%**	**62.50%**
Change	**0**	**5**	**$46,807.84**	**$385.08**	**$13.76**	**10**	**140**

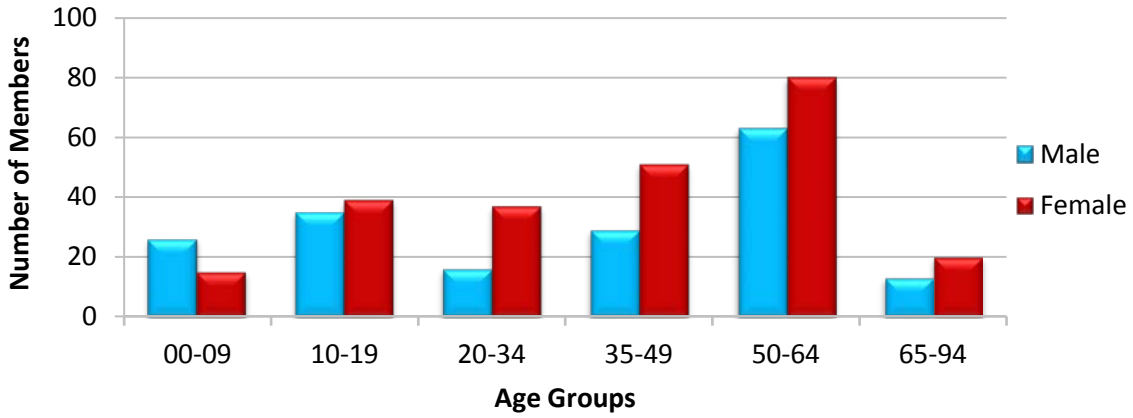
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Comparison of Calendar Years: Calcimimetics and Vitamin D Analogs

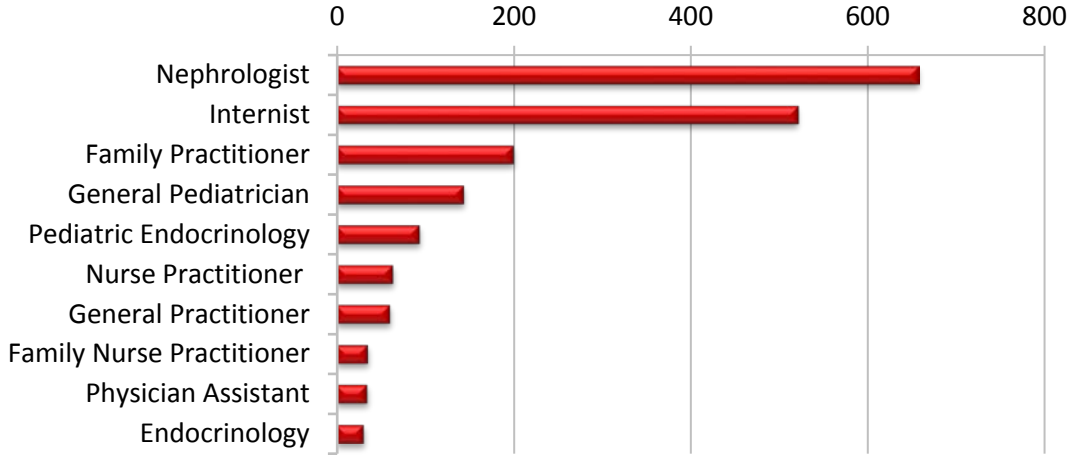
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	415	1,943	$758,641.63	$390.45	$10.79	75,975	70,299
2016	423	1,924	$805,037.44	$418.42	$10.74	82,340	74,975
% Change	**1.90%**	**-1.00%**	**6.10%**	**7.20%**	**-0.50%**	**8.40%**	**6.70%**
Change	**8**	**-19**	**$46,395.81**	**$27.97**	**-$0.05**	**6,365**	**4,676**

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

Demographics of Members Utilizing Natpara®, Calcimimetics, and Vitamin D Analogs

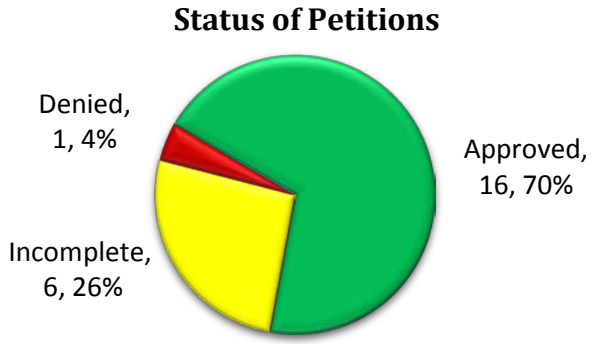


Top Prescriber Specialties of Natpara®, Calcimimetics, and Vitamin D Analogs by Number of Claims



Prior Authorization of Natpara®, Calcimimetics, and Vitamin D Analogs

There were 23 prior authorization requests submitted for Natpara®, Calcimimetics, and Vitamin D analogs during calendar year 2016. Of those, there were 2 prior authorization requests submitted for Natpara® for two unique members during calendar year 2016. The following chart shows the status of the submitted petitions.



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

Anticipated Patent/Exclusivity Expiration(s):

- Sensipar® (cinacalcet tablets): September 2026
- Rayaldee® (calcifediol extended-release [ER] capsules): August 2028
- Parsabiv™ (etelcalcetide injection): July 2030

New Drug Approval(s):

- Rayaldee® (calcifediol ER capsules): June 2016
- Parsabiv™ (etelcalcetide injection): February 2017

New Indication Approval(s):

- **October 2016:** The U.S. Food and Drug Administration (FDA) approved an expanded indication for Zemplar® (paricalcitol capsules) to be used in pediatric patients 10 years and older for the prevention of secondary hyperparathyroidism (SHPT) associated with chronic kidney disease (CKD) stages 3 and 4 and CKD stage 5 in patients on hemodialysis or peritoneal dialysis. Zemplar® was originally FDA approved for the same indications for use in adult patients in May of 2005.

Pipeline:

- **June 2017:** Amgen is currently recruiting for an open-label single dose study for use of Parsabiv™ (etelcalcetide) in pediatric patients 2 years of age to 18 years of age with SHPT receiving dialysis to evaluate the safety and pharmacokinetics in this population.

Guideline Update(s):

- **August 2016:** The updated Kidney Disease: Improving Global Outcomes (KDIGO) practice guideline on the management of chronic kidney disease-mineral and bone disorder (CKD-MBD) is anticipated to be released in the second quarter of 2017, however, a public review draft was issued in August of 2016. This will be the first update since the 2009 KDIGO CKD-MBD guidelines were published. The 2016 draft update no longer recommends routine use of calcitriol or its analogs in CKD stages 3A to 5 in adult patients on dialysis. The recommendations state it is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD stages 4 to 5 with severe and progressive hyperparathyroidism. In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. It is important to note that these recommendations are not graded. In patients with CKD

stage 5D, the draft also recommends requiring parathyroid hormone (PTH)-lowering therapy; the guidelines suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs (*2B* grade recommendation).

Rayaldee® (Calcifediol Extended-Release Capsules) Product Summary[8,9]

Indication(s): Rayaldee® (calcifediol extended-release [ER] capsules) is a vitamin D_3 analog indicated for the treatment of SHPT in adults with CKD stage 3 or 4 and serum total 25-hydroxyvitamin D levels less than 30ng/mL.

- Limitations of Use: Rayaldee® is not indicated in patients with CKD stage 5 or end-stage renal disease on dialysis.

Dosing:

- Rayaldee® is available as 30mcg extended-release, oral capsules.
- The recommended initial dosing for Rayaldee® is 30mcg by mouth once daily at bedtime. Serum calcium should be below 9.8mg/dL before initiating treatment.
- Serum calcium, phosphorus, 25-hydroxyvitamin D, and intact parathyroid hormone (iPTH) should be monitored three months after starting therapy or changing the dose.
- The Rayaldee® dose should be increased to 60mcg once daily after three months if iPTH is above the treatment goal. Serum calcium should be below 9.8mg/dL, phosphorus should be below 5.5mg/dL, and 25-hydroxyvitamin D should be below 100ng/mL before increasing the dose.
- The dose of Rayaldee® should be suspended if iPTH is persistently abnormally low, serum calcium is consistently above the normal range, or serum 25-hydroxyvitamin D is consistently above 100ng/mL.

Mechanism of Action: Calcifediol (25-hydroxyvitamin D_3) is a prohormone of the active form of vitamin D_3, calcitriol (1,25-dihydroxyvitamin D_3). Calcifediol is converted to calcitriol by cytochrome P450 27B1 (CYP27B1), also called 1-alpha hydroxylase, primarily in the kidney. Calcitriol binds to the vitamin D receptor in target tissues and activates vitamin D responsive pathways that result in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis.

Contraindications:

- None.

Warnings and Precautions:

- Hypercalcemia: Excessive administration of vitamin D compounds, including Rayaldee®, can cause hypercalcemia and hypercalciuria. Severe hypercalcemia due to substantial overdosage of vitamin D and its metabolites may require emergency attention. Patients should be informed about the symptoms of elevated calcium.
- Digitalis Toxicity: Hypercalcemia of any cause increases the risk of digitalis toxicity. In patients using Rayaldee® concomitantly with digitalis compounds, serum calcium and signs and symptoms of digitalis toxicity should be monitored more frequently when initiating or adjusting the dose of Rayaldee®.

- Adynamic Bone Disease: Patients should be monitored for abnormally low levels of iPTH levels when using Rayaldee®, and the dose should be adjusted if needed.

Adverse Reactions: The most common adverse reactions (≥ 3% and more frequent than placebo) were anemia, nasopharyngitis, increased blood creatinine, dyspnea, congestive heart failure, and constipation.

Drug Interactions:

- Co-administration of cytochrome P450 inhibitors, such as ketoconazole, may alter serum levels of calcifediol.
- Co-administration of thiazides may cause hypercalcemia.
- Cholestyramine may impair the absorption of calcifediol.
- The half-life of calcifediol is reduced by drugs stimulating microsomal hydroxylation, such as phenobarbital or other anticonvulsants.

Use in Specific Populations:

- Pregnancy Category C: Calcifediol has been shown to be teratogenic in rabbits when given in doses of 8 to 16 times the human dose of 60mcg/day, based on body surface area. There are no adequate and well-controlled studies in pregnant women. Rayaldee® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Labor and Delivery: The effect of Rayaldee® on the mother and fetus during labor and delivery is not known.
- Nursing Mothers: Limited available evidence indicates that calcifediol is poorly excreted in human milk. Caution should be exercised when Rayaldee® is administered to a nursing woman.
- Pediatric Use: The safety and efficacy of Rayaldee® have not been established in pediatric patients.
- Geriatric Use: Of the total number of subjects in Phase 3 placebo-controlled clinical studies of Rayaldee®, 63% were ≥ 65 years of age and 22% were ≥ 75 years of age. No overall differences in the safety or efficacy of Rayaldee® were observed between subjects older than 65 years and younger subjects.
- Renal Impairment: No difference in efficacy was observed between patients with CKD stage 3 or those with stage 4 disease in a subgroup analysis. Safety outcomes were similar in these subgroups. The safety and efficacy of Rayaldee® in the treatment of secondary hyperparathyroidism in patients with CKD stage 2 or stage 5 and patients with end-stage renal disease on dialysis have not been established.
- Overdosage: Excessive administration of Rayaldee® can cause hypercalciuria, hypercalcemia, hyperphosphatemia, or over suppression of iPTH. Common symptoms of vitamin D overdosage may include constipation, decreased appetite, dehydration, fatigue, irritability, muscle weakness, or vomiting. Treatment of acute accidental overdosage with Rayaldee® should consist of general supportive measures. If the overdosage is discovered within a short time, emesis should be induced or gastric lavage performed to prevent further absorption. Serial serum and urine calcium measurements should be obtained, and any electrocardiographic abnormalities due to hypercalcemia

assessed. Supplemental calcium should be discontinued. Standard medical treatment should be considered if persistent and markedly elevated serum calcium levels occur. Calcifediol is not significantly removed by dialysis.

Efficacy: The efficacy and safety of Rayaldee® were evaluated in two randomized, double-blind, placebo-controlled trials in 429 patients with SHPT and CKD stage 3 or 4 with serum total 25-hydroxyvitamin D levels between 10 and 30ng/mL. The primary analysis compared the proportion of individuals who experienced at least a 30% reduction in plasma iPTH from baseline to the end of the trial.

- A larger proportion of patients randomized to Rayaldee® experienced at least a 30% reduction in plasma iPTH from baseline compared to placebo in both trials (33% vs. 8% in the first trial [p<0.001] and 34% vs. 7% in the second trial [p<0.001]).
- Serum total 25-hydroxyvitamin D levels increased to at least 30ng/mL in 80% and 83% of subjects treated with Rayaldee® vs. 3% and 7% of patients treated with placebo (p<0.001) in the two studies, respectively.

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month	Cost Per Year
Rayaldee® (calcifediol ER) 30mcg capsule◊	**$30.93**	**$1,855.80**	**$22,269.60**
calcitriol 0.5mcg capsule+	$0.77	$23.10	$277.20
doxercalciferol 1mcg capsule±	$12.00	$360.00	$4,320.00

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.
Unit = capsule
+Calcitriol dose based on 0.5mcg daily.
±Doxercalciferol recommended initial dose for predialysis patients is 1mcg per day.
◊Rayaldee® dose based on 60mcg per day.

Parsabiv™ (Etelcalcetide Injection) Product Summary[10,11]

Indication(s): Parsabiv™ (etelcalcetide injection) is a calcium-sensing receptor agonist indicated for SHPT in adult patients with CKD on hemodialysis.

- Limitations of Use: Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism (HPT), or in patients with CKD who are not on hemodialysis, and Parsabiv™ is not recommended for use in these populations.

Dosing:

- Parsabiv™ is available in three strengths in single-dose vials for injection: 2.5mg/0.5mL, 5mg/mL, and 10mg/2mL.
- Corrected serum calcium should be at or above the lower limit of normal prior to initiation, dose increases, or re-initiation of Parsabiv™.
- The recommended starting dose of Parsabiv™ is 5mg administered by intravenous (IV) bolus injection three times per week at the end of hemodialysis treatment.
- The maintenance dose is individualized and determined by titration based on PTH and corrected serum calcium response. The dose range is 2.5mg to 15mg three times per week.

- The dose may be increased in 2.5mg or 5mg increments no more frequently than every four weeks.
- Serum calcium should be measured within one week after initiation or dose adjustment and every four weeks for maintenance.
- PTH should be measured four weeks after initiation or dose adjustment.
- The Parsabiv™ dose should be decreased or temporarily discontinued in individuals with PTH levels below the target range.
- Consideration should be given to decreasing or temporarily discontinuing Parsabiv™ or use of concomitant therapies to increase corrected serum calcium in patients with a corrected serum calcium below the lower limit of normal but at or above 7.5mg/dL without symptoms of hypocalcemia.
- Parsabiv™ should be stopped and hypocalcemia treated if the corrected serum calcium falls below 7.5mg/dL or if patients report symptoms of hypocalcemia.
- Parsabiv™ should not be mixed or diluted prior to administration.
- Parsabiv™ should be administered by IV bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse back or intravenously after rinse back.

Mechanism of Action: Etelcalcetide is a calcimimetic agent that allosterically modulates the calcium-sensing receptor (CaSR). Etelcalcetide binds to the CaSR and enhances activation of the receptor by extracellular calcium. Activation of the CaSR on parathyroid chief cells decreases PTH secretion.

Contraindications:

- Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients.

Warnings and Precautions:

- Hypocalcemia: Severe hypocalcemia can cause paresthesias, myalgias, muscle spasms, seizures, QT prolongation, and ventricular arrhythmias. Patients predisposed to QT interval prolongation, ventricular arrhythmias, and seizures may be at increased risk and require close monitoring. Patients should be educated on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.
- Worsening Heart Failure: Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to Parsabiv™ could not be completely excluded. Patients should be closely monitored for worsening signs and symptoms of heart failure.
- Upper Gastrointestinal (GI) Bleeding: Patients with risk factors for upper GI bleeding may be at increased risk. Patients should be monitored, promptly evaluated, and treated for any suspected GI bleeding.
- Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of Parsabiv™ should be reduced or discontinued.

Adverse Reactions: The most common adverse reactions (≥ 5%) were decreased blood calcium, muscle spasms, diarrhea, nausea, vomiting, headache, hypocalcemia, and paresthesia.

Use in Specific Populations:

- Pregnancy: There are no available data on the use of Parsabiv™ in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered Parsabiv™ during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15mg three times per week. In embryo-fetal studies, when rats and rabbits were administered Parsabiv™ during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.
- Lactation: Parsabiv™ is not recommended while breastfeeding. There are no data regarding the presence of Parsabiv™ in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma.
- Pediatric Use: The safety and efficacy of Parsabiv™ have not been established in pediatric patients.
- Geriatric Use: Of the 503 patients in placebo-controlled studies who received Parsabiv™, 177 patients (35.2%) were ≥ 65 years of age and 72 patients (14%) were ≥ 75 years of age. No clinically significant differences in safety, efficacy, or plasma concentrations were observed between patients ≥ 65 years of age and younger patients (≥ 18 and < 65 years of age).
- Overdosage: There is no clinical experience with Parsabiv™ overdosage. Overdosage of Parsabiv™ may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although Parsabiv™ is cleared by dialysis, hemodialysis has not been studied as a treatment for Parsabiv™ overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken.

Efficacy: The safety and efficacy of Parsabiv™ for the treatment of SHPT were evaluated in two 26-week randomized, double-blind, placebo-controlled trials enrolling 1,023 SHPT patients with CKD on hemodialysis. The primary outcome measure in both studies was the proportion of patients with > 30% reduction in PTH levels from baseline during the efficacy assessment phase (weeks 20 through 27).

- In both studies, a significantly higher proportion of patients treated with Parsabiv™ achieved the primary endpoint vs. placebo patients (Study 1: 77% vs. 11%; Study 2: 79% vs. 11%; $p<0.001$ for both studies).
- In both studies, significantly more Parsabiv™-treated patients achieved PTH levels < 300pg/mL compared to placebo patients (Study 1: 52% vs. 6%; Study 2: 56% vs. 5%; $p < 0.001$ for both studies).

- In both studies, a significantly greater reduction in mean PTH, corrected serum calcium, and serum phosphate levels from baseline were achieved in the Parsabiv™-treated patients vs. placebo-treated patients.

Cost: Cost and launch information are not available at this time.

Zemplar® (Paricalcitol Capsules) Product Summary[12]

Indication(s): Zemplar® (paricalcitol capsules) is a vitamin D analog indicated in adults and pediatric patients 10 years of age and older for the prevention and treatment of SHPT associated with CKD stages 3 and 4 and CKD stage 5 in patients on hemodialysis or peritoneal dialysis.

Dosing:

- Zemplar® is available as 1mcg and 2mcg oral capsules and as an intravenous solution in the following strengths: 2mcg/mL and 5mcg/mL.
- The recommended initial dosing in CKD stages 3 and 4 for Zemplar® is dependent on baseline iPTH level in adults:
  - For iPTH ≤ 500pg/mL: 1mcg orally daily or 2mcg three times a week.
  - For iPTH > 500pg/mL: 2mcg orally daily or 4mcg three times a week.
  - In pediatric patients 10 to 16 years of age: 1mcg orally three times a week.
- The recommended initial adult dosing in CKD stage 5 for Zemplar® is calculated by baseline iPTH divided by 80 and administered three times a week. In ages 10 to 16 years, the dose is determined by baseline iPTH divided by 120 and administered three times a week.
- For Zemplar® three times a week dosing, the dose should be given no more frequently than every other day.
- Zemplar® dose titration is based on change in iPTH relative to baseline (*See prescribing information for specific titration and dose adjustments*).
- In CKD stage 5, patients should only be treated after their baseline serum calcium has been reduced to 9.5mg/dL or lower to avoid hypercalcemia.

Mechanism of Action: Paricalcitol is a synthetic, biologically active vitamin D_2 analog of calcitriol. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the vitamin D receptor, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce PTH levels by inhibiting PTH synthesis and secretion.

Contraindications:

- Evidence of hypercalcemia
- Evidence of vitamin D toxicity

Warnings and Precautions:

- Hypercalcemia: Excessive administration of Zemplar® capsules can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic

bone disease. Prescription-based doses of vitamin D and its derivatives should be withheld during Zemplar® treatment.

- Digitalis Toxicity: Digitalis toxicity is potentiated by hypercalcemia of any cause. Caution should be exercised when Zemplar® capsules are prescribed concomitantly with digitalis compounds.
- Laboratory Tests: Serum calcium, serum phosphorus, and serum or plasma iPTH should be monitored during initial dosing or following any dose adjustment. Zemplar® capsules may increase serum creatinine and therefore decrease the estimated glomerular filtration rate (eGFR).
- Aluminum Overload and Toxicity: Excessive use of aluminum containing compounds should be avoided.

Adverse Reactions: The most common adverse reactions (> 5% and more frequent than placebo) include diarrhea, nasopharyngitis, dizziness, vomiting, hypertension, hypersensitivity, nausea, and edema.

Drug Interactions:

- Strong CYP3A Inhibitors: Strong CYP3A inhibitors (e.g. ketoconazole) will increase the exposure of Zemplar® and should be used with caution.
- Cholestyramine or Mineral Oil: Intestinal absorption of Zemplar® may be reduced if administered simultaneously with cholestyramine or mineral oil. Zemplar® capsules should be administered at least 1 hour before or 4 to 6 hours after taking cholestyramine or mineral oil.

Use in Specific Populations:

- Pregnancy: Limited data with Zemplar® capsules in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with CKD in pregnancy.
- Nursing Mothers: Because of the potential for serious adverse reactions, including hypercalcemia in a breastfed infant, patients should be advised that breastfeeding is not recommended during treatment with Zemplar®.
- Pediatric Use: The safety and effectiveness of Zemplar® capsules have been established in pediatric patients 10 to 16 years of age for the prevention and treatment of SHPT associated with CKD stage 3, 4, and 5.
- Geriatric Use: Of the total number (n=220) of CKD stages 3 and 4 patients in clinical studies of Zemplar® capsules, 49% were age 65 and older, while 17% were age 75 and older. Of the total number (n=88) of CKD stage 5 patients in the pivotal study of Zemplar® capsules, 28% were age 65 and older, while 6% were age 75 and older. No overall differences in safety and effectiveness were observed between these patients and younger patients.
- Overdosage: Excessive administration of Zemplar® capsules can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and over suppression of PTH. The treatment of acute overdosage of Zemplar® capsules should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed

through the stomach, the administration of mineral oil may promote its fecal elimination. Zemplar® is not significantly removed by dialysis.

Efficacy (Zemplar® Capsules):

- **Adults with CKD Stage 3 and 4:** Three, 24-week, double blind, placebo-controlled, randomized, multicenter Phase 3 clinical studies in CKD stage 3 and 4 with a total of 107 patients receiving Zemplar® capsules and 113 patients receiving placebo were evaluated. The overall average weekly dose of Zemplar® capsules was 9.6mcg/week in the daily regimen and 9.5mcg/week in the three times a week regimen. The primary efficacy endpoint of at least two consecutive ≥ 30% reductions from baseline iPTH was achieved by 91% of the Zemplar® capsule group versus 13% of the placebo-treated patients ($p<0.001$).
- **Pediatric Patients 10 to 16 Years of Age:** The safety and efficacy of Zemplar® capsules was evaluated in a 12-week, double blind, placebo-controlled, randomized, multicenter clinical study in CKD stage 3 and 4 patients 10 to 17 years of age. A total of 18 patients received Zemplar® capsules and 18 patients received placebo during the blinded phase of the study. The primary efficacy endpoint of at least two consecutive ≥ 30% reductions from baseline iPTH was achieved by 28% of the Zemplar® capsule group versus 0% of the placebo-treated patients ($p<0.05$).
- **Adults with CKD Stage 5:** The efficacy and safety of Zemplar® capsules were evaluated in a 12-week, double blind, placebo-controlled, randomized, multicenter Phase 3 clinical study in CKD stage 5 patients on hemodialysis or peritoneal dialysis. A with a total of 61 patients received Zemplar® capsules and 27 patients received placebo. The overall average weekly dose of Zemplar® capsules was 9.6mcg/week in the daily regimen and 9.5mcg/week in the three times a week regimen. The primary efficacy endpoint of at least two consecutive ≥ 30% reductions from baseline iPTH was achieved by 88% of the Zemplar® capsule group versus 13% of the placebo-treated patients. The proportion of patients meeting the primary efficacy endpoint was similar for both hemodialysis and peritoneal dialysis patients.

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month	Cost Per Year
paricalcitol 1mcg capsules[£]	**$5.59**	**$167.70**	**$2,012.40**
paricalcitol 2mcg capsules[£]	**$11.76**	**$352.80**	**$4,233.60**
paricalcitol 5mcg/mL injection[+]	$10.50	$252.00	$3,024.00
calcitriol 0.5mcg capsule[◊]	$0.77	$23.10	$277.20
doxercalciferol 2.5mcg capsule[±]	$19.08	$1,831.68	$21,980.16

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

Unit = capsule or mL

[£]Paricalcitol dosing based on 1mcg or 2mcg daily.

[+]The recommended starting dose for paricalcitol injection is 0.04mcg/kg to 0.1mcg/kg while initial doses as high as 0.24mcg/kg (16.8mcg) have been administered safely. The cost is based on a dosing regimen of 10mcg three times per week.

[◊]Calcitriol dose based on 0.5mcg daily.

[±]The maximum recommended dose for doxercalciferol for patients receiving dialysis is 20mcg three times per week at dialysis.

Hectorol® (Doxercalciferol Capsules) Product Summary[13]

Indication(s): Hectorol® (doxercalciferol capsules) is a synthetic vitamin D_2 analog indicated for the treatment of SHPT in patients with CKD on dialysis and indicated in pre-dialysis patients for the treatment of SHPT in patients with CKD stage 3 or stage 4.

Dosing:

- Hectorol® (doxercalciferol) is available as 0.5mcg, 1mcg, and 2.5mcg oral capsules and as 2mcg/mL and 4mcg/2mL intravenous solution.
- The recommended initial dosing in dialysis patients for Hectorol® is 10mcg three times weekly at dialysis (approximately every other day).
    - The initial dose should be adjusted, as needed, in order to lower blood iPTH into range of 150 to 300pg/mL.
    - The dose may be increased at 8-week intervals by 2.5mcg if iPTH is not lowered by 50% and fails to reach the target range.
    - The maximum recommended dose is 20mcg three times a week at dialysis for a total of 60mcg per week.
    - The dose of Hectorol® should be suspended if iPTH falls below 100pg/mL and restarted one week later at a dose that is at least 2.5mcg lower than the last administered dose.
    - During titration, iPTH, serum calcium, and serum phosphorus levels should be obtained weekly.
    - If hypercalcemia, hyperphosphatemia, or a serum calcium times serum phosphorus product greater than $55mg^2/dL^2$ is noted, the dose of Hectorol® should be decreased or suspended and/or the dose of the phosphate binder should be adjusted.
    - Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels.
- The recommended initial dosing in pre-dialysis patients for Hectorol® is 1mcg once daily.
    - The initial dose should be adjusted, as needed, in order to lower blood iPTH to within target ranges.
    - The dose may be increased at 2-week intervals by 0.5mcg to achieve the target range of iPTH.
    - The maximum recommended dose of Hectorol® is 3.5mcg administered once daily.
    - Serum levels of calcium and phosphorus and plasma levels of iPTH should be monitored at least every two weeks for three months after initiation of Hectorol® therapy or following dose adjustments, then monthly for three months, and every three months thereafter.
    - If hypercalcemia, hyperphosphatemia, or a serum calcium times phosphorus product greater than $55mg^2/dL^2$ is noted, the dose of Hectorol® should be decreased or suspended and/or the dose of the phosphate binder should be adjusted.
    - Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels.

Mechanism of Action: Calcitriol regulates blood calcium at levels required for essential body functions. Specifically, the biologically active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney, and in conjunction with PTH, the mobilization of calcium from the skeleton. They act directly on osteoblasts to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion. These functions are mediated by the interaction of these biologically active metabolites with specific receptor proteins in the various target tissues. In patients with CKD, deficient production of biologically active vitamin D metabolites leads to SHPT, which contributes to the development of metabolic bone disease.

Contraindications:

- Hectorol® should not be given to patients with a tendency towards hypercalcemia or current evidence of vitamin D toxicity.

Warnings:

- Overdosage: Overdosage of any form of vitamin D, including Hectorol®, is dangerous. Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures, and may potentiate the action of digitalis drugs. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. The serum calcium times serum phosphorus (Ca X P) product should be maintained at $< 55\ mg^2/dL^2$ in patients with CKD. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition. Since doxercalciferol is a precursor for $1\alpha,25\text{-}(OH)_2D_2$, a potent metabolite of vitamin D_2, pharmacologic doses of vitamin D and its derivatives should be withheld during Hectorol® treatment to avoid possible additive effects and hypercalcemia.

Adverse Reactions: The most common adverse reactions reported in the dialysis study (> 5% and more frequent than placebo) included headache, malaise, bradycardia, nausea/vomiting, edema, dizziness, and dyspnea.

Drug Interactions:

- Specific drug interaction studies have not been conducted.
- Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; therefore, it may impair intestinal absorption of Hectorol®.
- Magnesium-containing antacids and Hectorol® should not be used concomitantly because such use may lead to the development of hypermagnesemia.
- The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of Hectorol®.
- Although not examined specifically, enzyme inducers (such as glutethimide and phenobarbital) may affect the 25-hydroxylation of Hectorol® and may necessitate dosage adjustments.
- CYP450 inhibitors (e.g. ketoconazole and erythromycin) may inhibit the 25-hydroxylation of Hectorol®. Hence, formation of the active Hectorol® moiety may be hindered.

Use in Specific Populations:

- Pregnancy Category B: Reproduction studies in rats and rabbits, at doses up to 20mcg/kg/day and 0.1mcg/kg/day (approximately 25 times and less than the maximum recommended human dose of 60mcg/week based on mcg/m^2 body surface area, respectively) have revealed no teratogenic or fetotoxic effects due to Hectorol®. There are, however, no adequate and well-controlled studies in pregnant women.
- Nursing Mothers: It is not known whether Hectorol® is excreted in human milk. Because other vitamin D derivatives are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Hectorol®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- Pediatric Use: The safety and efficacy of Hectorol® in pediatric patients have not been established.
- Geriatric Use: Of the 138 patients treated with Hectorol® capsules in two Phase 3 clinical studies, 30 patients were 65 years of age or older. In these studies, no overall differences in efficacy or safety were observed between patients 65 years of age or older and younger patients.
- Hepatic Insufficiency: Since patients with hepatic insufficiency may not metabolize Hectorol® appropriately, the drug should be used with caution in patients with impaired hepatic function. More frequent monitoring of iPTH, calcium, and phosphorus levels should be done in such individuals.

Efficacy (Hectorol® Capsules):

- **Adults with CKD Stage 5 on Dialysis:** Two, double-blind, placebo-controlled, multicentered clinical studies evaluated the safety and efficacy of Hectorol® capsules in 138 patients with CKD on hemodialysis. A total of 106 of the 138 patients who were treated with Hectorol® during the 16-week open-label phase achieved iPTH levels ≤ 300pg/mL. Additionally, 94 of these patients exhibited plasma iPTH levels ≤ 300pg/mL on at least three occasions; 87 patients had plasma iPTH levels < 150pg/mL on at least one occasion. Mean weekly doses during the open-label period in Study A ranged from 14.8mcg to 28.7mcg. In Study B, the mean weekly doses during the open-label period ranged from 19.2mcg to 28mcg. In both studies, iPTH levels increased progressively and significantly in 65.9% of the patients during the 8-week washout (control) period during which no vitamin D derivatives were administered. In contrast, Hectorol® treatment resulted in a statistically significant reduction from baseline in mean iPTH levels during the open-label treatment period in more than 93.5% of the 138 treated patients. During the double-blind period (weeks 17 to 24), the reduction in mean iPTH levels was maintained in the Hectorol® treatment group compared to a return to near baseline in the placebo group.
- **Adult with CKD Stage 3 to 4 Not on Dialysis:** Two clinical studies evaluated the safety and efficacy of Hectorol® capsules in 55 patients with CKD stage 3 or stage 4. The initial dose of Hectorol® was 1mcg per day. The dosage of Hectorol® was adjusted as necessary by the investigator in order to reduce iPTH levels to a target of ≥ 30% below post-washout baseline. The maximum dosage was limited to 3.5mcg per day. If at any time during the trial iPTH fell below 15pg/mL, Hectorol® was immediately suspended

and restarted at a lower dosage the following week. In analyses of pooled data from the two studies, iPTH levels decreased from baseline by an average of 101.4pg/mL in the Hectorol® group and by 4.4pg/mL in the placebo group (p<0.001). Greater reductions of iPTH with Hectorol® compared to placebo were observed in each study. Twenty (74%) of 27 subjects in the Hectorol® group achieved mean plasma iPTH suppression of ≥ 30% from baseline for the last four weeks of treatment, whereas two (7%) of the 28 subjects treated with placebo achieved this level of iPTH suppression. In the Hectorol®-treated patients, the reductions in plasma iPTH were associated with a reduction in serum bone-specific alkaline phosphatase.

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month	Cost Per Year
doxercalciferol 1mcg capsule[±]	**$12.00**	**$360.00**	**$4,320.00**
doxercalciferol 2.5mcg capsule[π]	**$19.08**	**$1,831.68**	**$21,980.16**
doxercalciferol 4mcg/2mL vial[¥]	$9.00	$108.00	$1,296.00
calcitriol 0.5mcg capsule[◊]	$0.77	$23.10	$277.20
paricalcitol 1mcg capsule[£]	$5.59	$167.70	$2,012.40
paricalcitol 2mcg capsule[£]	$11.76	$352.80	$4,233.60
paricalcitol 5mcg/mL injection[+]	$10.50	$252.00	$3,024.00

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC) or State Maximum Allowable Cost (SMAC) if NADAC unavailable.
Unit = capsule or mL
[£]Paricalcitol dosing based on 1mcg or 2mcg daily.
[+]The recommended starting dose for paricalcitol injection is 0.04mcg/kg to 0.1mcg/kg while initial doses as high as 0.24mcg/kg (16.8mcg) have been administered safely. The cost is based on a dosing regimen of 10mcg three times per week.
[◊]Calcitriol dose based on 0.5mcg daily.
[±]Doxercalciferol initial recommended dose for predialysis patients is 1mcg/day.
[π]The maximum dose for doxercalciferol for patients receiving dialysis is 20mcg three times per week at dialysis.
[¥]Doxercalciferol injection dose for a dialysis patient based on 4mcg three times/week at the end of dialysis.

Recommendations

The College of Pharmacy recommends the prior authorization of Rayaldee® (calcifediol ER capsules), Parsabiv™ (etelcalcetide), Zemplar® (paricalcitol capsules), and Hectorol® (doxercalciferol capsules) with the following criteria:

Rayaldee® (Calcifediol ER Capsules) Approval Criteria:

1. An FDA approved indication for treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease (CKD) stage 3 or 4; and
2. Member must not have CKD stage 5 or end-stage renal disease on dialysis; and
3. Member should have a serum total 25-hydroxyvitamin D level less than 30ng/mL before starting treatment; and
4. Member should have a serum calcium level below 9.8mg/dL before initiating treatment; and
5. Rayaldee® must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of secondary hyperparathyroidism; and

6. Member must have a documented failure or clinically-significant reason why the member cannot use available generic vitamin D analogs including calcitriol; and
7. Initial approval will be for 30mcg daily for three months.
    a. After three months, approval for 60mcg daily for 12 months can be considered if intact parathyroid hormone (iPTH) is above the treatment goal and serum calcium is below 9.8mg/dL, phosphorus is below 5.5mg/dL, and 25-hydroxyvitamin D is below 100ng/mL.
    b. Additional approvals will not be granted if iPTH is persistently abnormally low, serum calcium is consistently above the normal range, or serum 25-hydroxyvitamin D is consistently above 100ng/mL.
8. A quantity limit of 60 capsules per 30 days will apply.

Parsabiv™ (Etelcalcetide) Approval Criteria:

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

Zemplar® (Paricalcitol Capsules) Approval Criteria:

1. Member must be 10 years of age or older; and
2. An FDA approved indication for the prevention and treatment of secondary hyperparathyroidism (SHPT) associated with one of the following:
    a. Chronic kidney disease (CKD) stages 3 or 4; or
    b. CKD stage 5 in patients on hemodialysis or peritoneal dialysis; and
        i. Members with CKD stage 5 should have a corrected total serum calcium equal to or less than 9.5mg/dL before initiating treatment; and
3. Zemplar® must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of secondary hyperparathyroidism; and
4. Member must have a documented failure or a clinically-significant reason why the member cannot use available generic vitamin D analogs including calcitriol and Zemplar® injection;
5. A quantity limit of 30 capsules per 30 days will apply.

Hectorol® (Doxercalciferol Capsules) Approval Criteria:

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

Utilization Details of Calcimimetics and Vitamin D Analogs: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
CALCIMIMETIC PRODUCTS						
CINACALCET PRODUCTS						
SENSIPAR TAB 30MG	215	64	$185,532.31	$25.32	$862.94	23.05%
SENSIPAR TAB 60MG	140	35	$351,622.49	$74.39	$2,511.59	43.68%
SENSIPAR TAB 90MG	44	16	$148,100.87	$85.12	$3,365.93	18.40%
SUBTOTAL	**399**	**86***	**$685,255.67**	**$49.67**	**$1,717.43**	**85.13%**
VITAMIN-D ANALOG PRODUCTS						
CALCITRIOL PRODUCTS						
CALCITRIOL CAP 0.25MCG	826	215	$18,163.43	$0.53	$21.99	2.26%
CALCITRIOL CAP 0.5MCG	346	91	$15,827.64	$1.12	$45.74	1.97%
CALCITRIOL SOL 1MCG/ML	128	37	$22,991.23	$4.29	$179.62	2.86%
SUBTOTAL	**1,300**	**320***	**$56,982.30**	**$1.06**	**$43.83**	**7.09%**
PARICALCITOL PRODUCTS						
PARICALCITOL CAP 1 MCG	134	603	$21,387.33	$33.17	$1,119.37	2.66%
PARICALCITOL CAP 2 MCG	50	377	$16,190.41	$37.92	$1,259.06	2.01%
PARICALCITOL CAP 4 MCG	18	336	$8,864.55	$32.45	$1,026.78	1.08%
SUBTOTAL	**202**	**36***	**$46,262.29**	**$6.86**	**$229.02**	**5.75%**
DOXERCALCIFEROL PRODUCTS						
DOXERCALCIF CAP 1MCG	13	1	$8,232.35	$22.62	$633.26	1.02%
DOXERCALCIF CAP 2.5MCG	10	1	$8,304.83	$27.68	$830.48	1.03%
SUBTOTAL	**23**	**2***	**$16,537.18**	**$24.91**	**$719.01**	**2.05%**
TOTAL	**1,924**	**423***	**$805,037.44**	**$10.74**	**$418.42**	**100%**

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

Utilization Details of Natpara® (Parathyroid Hormone Injection): Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
PARATHYROID HORMONE ANALOG PRODUCTS						
PARATHYOID HORMONE PRODUCTS						
NATPARA INJ 100MCG	13	1	$113,690.80	$312.34	$8,745.45	100%
TOTAL	**13**	**1***	**$113,690.80**	**$312.34**	**$8,745.45**	**100%**

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

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Appendix N

Calendar Year 2016 Annual Review of Opioid Analgesics and Opioid Medication Assisted Treatment (MAT) Medications & 30-Day Notice to Prior Authorize Arymo™ ER (Morphine Sulfate Extended-Release), Troxyca® ER (Oxycodone/Naltrexone Extended-Release), Vantrela™ ER (Hydrocodone Extended-Release), Oxaydo® (Oxycodone), and RoxyBond™ (Oxycodone)

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Opioid Analgesics*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Long-Acting: oxycodone ER 10mg, 15mg, 20mg only (Oxycontin®)◊ **Short-Acting:** ASA/butalbital/caffeine/codeine (Fiorinal with Codeine®) codeine codeine/APAP dihydrocodone/ASA/ caffeine (Synalgos-DC®) hydrocodone/APAP (Norco®) hydrocodone/IBU (Vicoprofen®, Ibudone®, Reprexain™) hydromorphone (Dilaudid®) morphine IR (MSIR®) oxycodone IR (Oxy IR®) oxycodone/APAP (Percocet®) oxycodone/ASA (Percodan®) oxycodone/IBU (Combunox™) tramadol/APAP (Ultracet®) tramadol (Ultram®)	**Long-Acting:** buprenorphine (Butrans®) fentanyl patches (Duragesic®) hydrocodone ER (Hysingla™ ER) morphine ER tablets (MS Contin®) oxycodone ER (Oxycontin®)◊ **Short-Acting:** oxymorphone IR (Opana®) tapentadol IR (Nucynta®)	**Long-Acting:** buprenorphine ER buccal film (Belbuca™) hydrocodone ER (Zohydro™ ER) hydromorphone ER (Exalgo®) methadone (Dolophine®) morphine sulfate ER (Kadian®) morphine sulfate ER (MorphaBond™) morphine/naltrexone (Embeda®) oxycodone ER (Xtampza™ ER) oxymorphone (Opana® ER)+ tapentadol ER (Nucynta® ER) tramadol ER (Ultram ER®, Ryzolt®) **Short-Acting:** hydrocodone/APAP (Xodol®, Zamicet®, Liquicet®) oxycodone (Oxecta®) oxycodone/APAP (Primlev™, Xolox®)	**Long-Acting:** oxycodone/APAP ER (Xartemis™ XR) **Oncology Only:** fentanyl transmucosal lozenge (Actiq®) fentanyl buccal tablet (Fentora®) fentanyl buccal film (Onsolis®) fentanyl sublingual tablet (Abstral®) fentanyl nasal spray (Lazanda®) fentanyl sublingual spray (Subsys™)

APAP = Acetaminophen, ASA = Aspirin, IR = Immediate-Release, ER = Extended-Release, IBU = Ibuprofen
*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
◊Brand name preferred.
+Brand name Opana® ER preferred. Generic oxymorphone ER tablets require special authorization as they are not abuse-deterrent.

- Tier-1 products are covered with no prior authorization necessary.
- Members with an oncology-related diagnosis are exempt from the prior authorization process, and do not require pain contracts.
- Only one long-acting and one-short acting agent can be used concurrently. Short-acting,

solid dosage formulation products are limited to a quantity of four units per day or a quantity of 120 units per 30 days.

- An age restriction applies on oral liquid narcotic analgesic products for all members older than 12 years of age and oral solid dosage forms for all members younger than 10 years of age.

Opioid Analgesics Tier-2 Approval Criteria:

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

Opioid Analgesics Tier-3 Approval Criteria:

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

Special PA Approval Criteria:

1. Actiq®, Fentora®, Onsolis®, Abstral®, Lazanda®, and Subsys™ are approved for oncology-related diagnoses only.
2. Authorization of unique strengths of hydrocodone/acetaminophen require a patient-specific, clinically significant reason the member cannot use generic Norco® (hydrocodone/APAP 5/325mg, 7.5/325mg, or 10/325mg).

Xartemis™ XR (Oxycodone/APAP) Extended-Release Tablets Approval Criteria:

1. An acute pain condition requiring around-the-clock opioid treatment; and
2. A patient-specific, clinically significant reason for all of the following:
    a. Why the member cannot use any other opioid medication for treatment of acute pain; and
    b. Why the member requires a long-acting medication for an acute pain condition; and
    c. Why the member cannot use Oxycontin® (oxycodone extended-release) and over-the-counter (OTC) acetaminophen individual products in place of this combination product; and
3. A quantity limit of four tablets per day will apply with a maximum approval duration of 10 days; and
4. The member must not exceed 3,250mg of acetaminophen per day from all sources; and
5. Tier structure rules still apply.

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

1. Members may be approved for greater than 12 claims per year of hydrocodone products if the member has a pain contract with a single prescriber. A copy of the pain contract should be submitted with the prior authorization requests. Requests outside of the plan outlined in the contract will not be approved.

2. Members with a current oncology-related diagnosis or hemophilia diagnosis do not require a pain contract for additional approvals.

Suboxone® (Buprenorphine/Naloxone Sublingual Tablets and Film), Subutex® (Buprenorphine Sublingual Tablets), Zubsolv® (Buprenorphine/Naloxone Sublingual Tablets) and Bunavail™ (Buprenorphine/Naloxone Buccal Films) Approval Criteria:

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

High-Dose Buprenorphine Products Approval Criteria:

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

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

Probuphine® (Buprenorphine Implant) Approval Criteria:

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

Utilization of Opioid Analgesics and MAT Medications: Calendar Year 2016

Comparison of Calendar Years: Opioid Analgesics

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	124,583	447,867	$18,082,397.65	$40.37	$2.14	31,415,189	8,466,222
2016	116,540	416,553	$18,061,118.28	$43.36	$2.26	29,345,261	7,996,073
% Change	**-6.50%**	**-7.00%**	**-0.10%**	**7.40%**	**5.60%**	**-6.60%**	**-5.60%**
Change	**-8,043**	**-31,314**	**-$21,279.37**	**$2.99**	**$0.12**	**-2,069,928**	**-470,149**

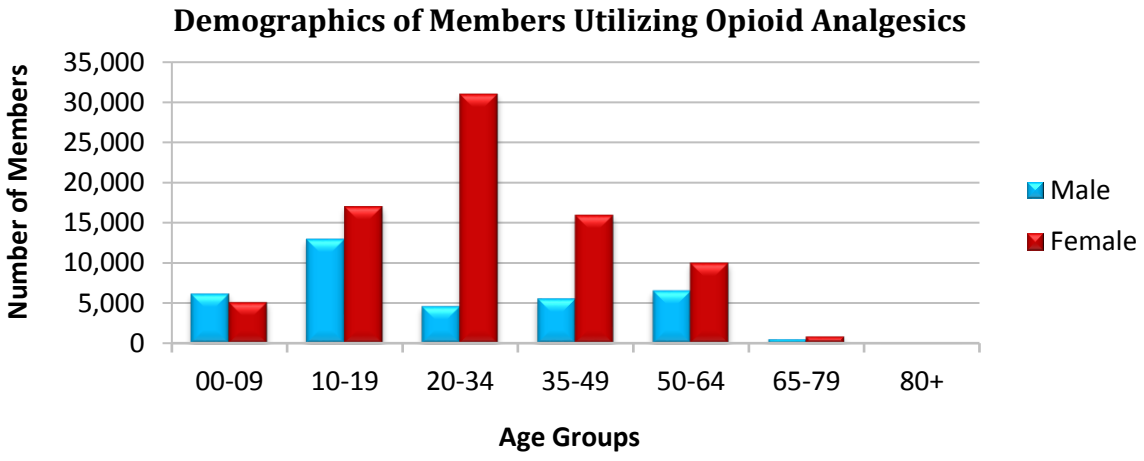
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Butrans® and Belbuca™ are included in the opioid analgesics data as they are only indicated for chronic pain and not for the treatment of opioid dependence.

Comparison of Calendar Years: MAT Medications

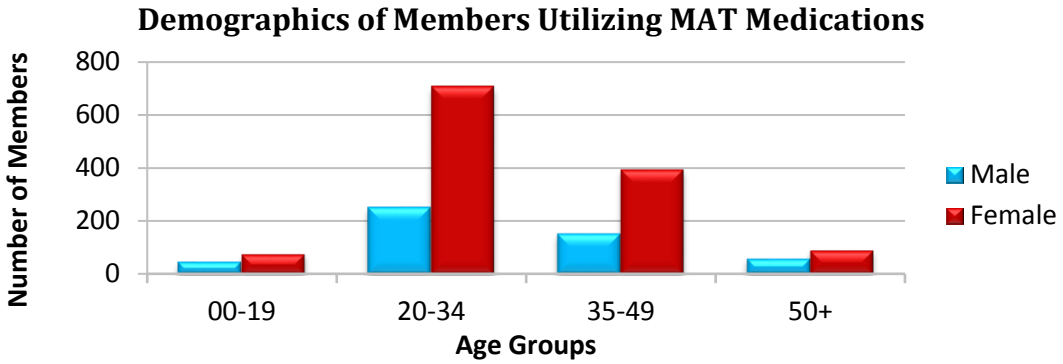
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	1,419	10,062	$3,398,032.29	$337.71	$12.54	558,213	271,017
2016	1,780	13,109	$4,334,358.66	$330.64	$12.70	707,352	341,381
% Change	**25.40%**	**30.30%**	**27.60%**	**-2.10%**	**1.30%**	**26.70%**	**26.00%**
Change	**361**	**3,047**	**$936,326.37**	**-$7.07**	**$0.16**	**149,139**	**70,364**

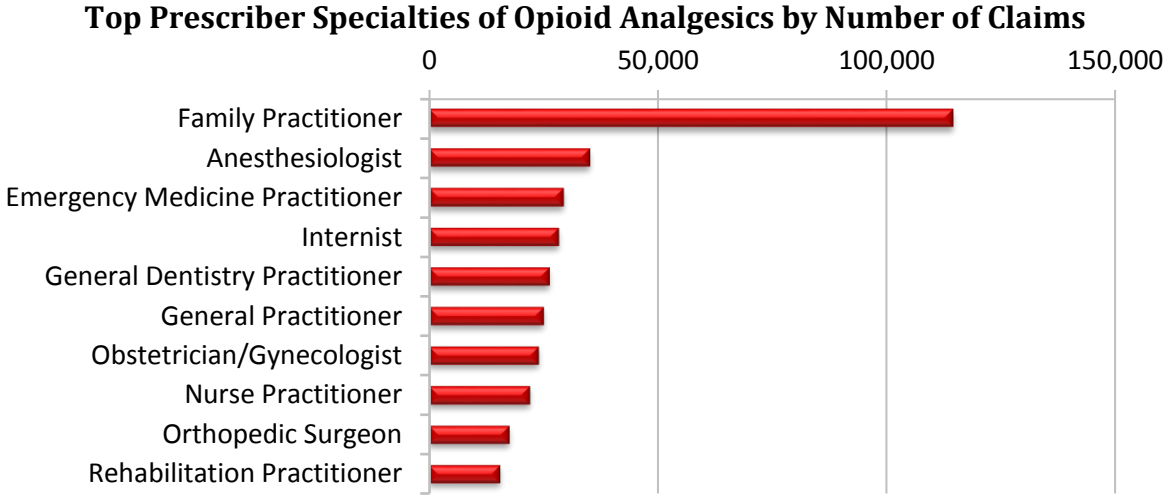
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Does not include Butrans® or Belbuca™ claims.

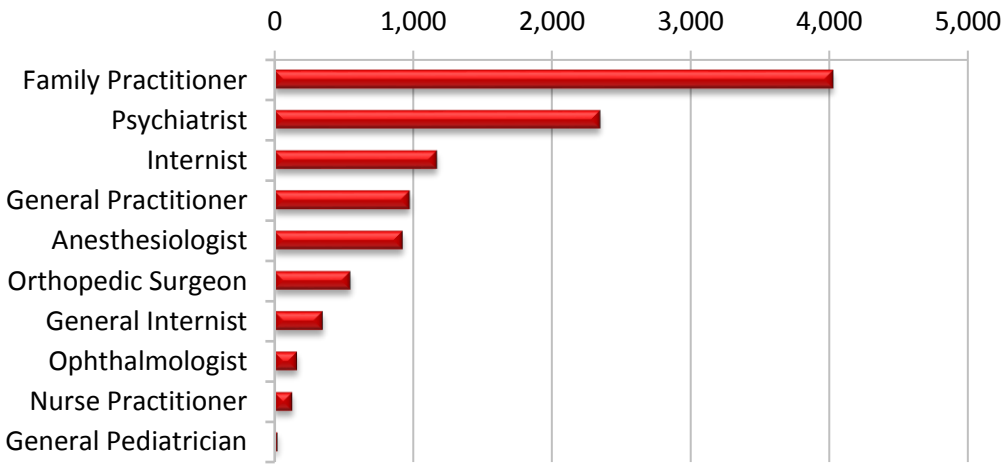
- Aggregate drug rebates collected during calendar year 2016 for opioid analgesics and MAT medications: $8,760,054.48[Δ]



[Δ] Important considerations: Aggregate drug rebates are based on the date the claim is paid rather than the date dispensed. Claims data are based on the date dispensed. Both claims data and aggregated drug rebates do not include Indian Health Service providers.

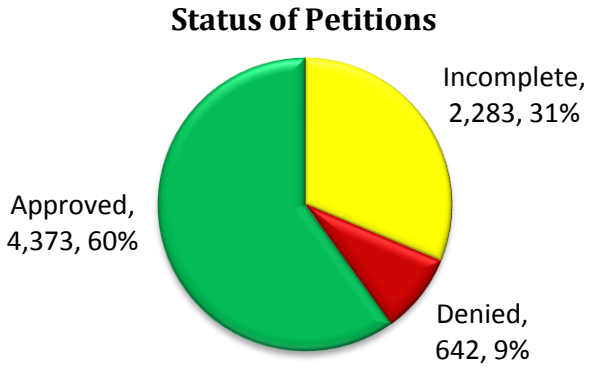




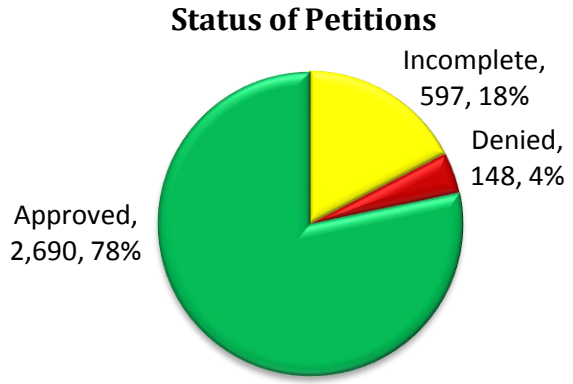


Prior Authorization of Opioid Analgesics & MAT Medications

There were 7,298 prior authorizations submitted for the opioid analgesics category during calendar year 2016. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.



There were 3,435 prior authorizations submitted for MAT medications during calendar year 2016. Computer edits are in place to detect diagnosis, concomitant opioid claims, and quantities/day supply and generate automated prior authorizations where possible. The following chart shows the status of the submitted 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]

Anticipated Patent Expiration(s):

- Butrans® (buprenorphine transdermal system): September 2017
- Abstral® (fentanyl sublingual tablet): September 2019
- Probuphine® (buprenorphine implant): April 2024
- Lazanda® (fentanyl nasal spray): October 2024
- Nucynta® (tapentadol immediate-release [IR] tablets): June 2025
- Xtampza™ ER (oxycodone extended-release [ER] capsules): June 2025
- Belbuca™ (buprenorphine ER buccal film): July 2027
- Fentora® (fentanyl buccal tablet): June 2028
- MorphaBond™ (morphine ER tablets): August 2028
- Nucynta® ER (tapentadol ER tablets): September 2028
- Embeda® (morphine/naltrexone ER tablets): November 2029
- Subsys™ (fentanyl sublingual spray): April 2030
- Hysingla™ ER (hydrocodone bitartrate ER tablets): December 2031
- Xartemis™ XR (oxycodone/acetaminophen[APAP] ER tablets): May 2032
- Zubsolv® (buprenorphine/naloxone sublingual tablets): September 2032
- Zohydro™ ER (hydrocodone bitartrate ER): September 2034
- Bunavail™ (buprenorphine/naloxone buccal films): April 2035

New Drug Approval(s):

- **December 2015:** Oxaydo® (oxycodone tablets)
- **August 2016:** Troxyca® ER (oxycodone/naltrexone ER capsules)
- **January 2017:** Arymo™ ER (morphine sulfate ER tablets)
- **January 2017:** Vantrela™ ER (hydrocodone ER tablets)
- **April 2017:** RoxyBond™ (oxycodone tablets)

New Indication(s):

- **May 2017:** The U.S. Food and Drug Administration (FDA) expanded the indication for Bunavail™ (buprenorphine/naloxone buccal films) to include induction or the initiation of buprenorphine treatment for opioid dependence; Bunavail™ was previously FDA approved for the maintenance treatment of opioid dependence in 2015.

Drug Update(s):

- **August 2015:** A generic formulation of Trezix® (dihydrocodeine/APAP/caffeine) became available. Trezix® is supplied as 320.5mg APAP/30mg caffeine/16mg dihydrocodeine oral capsules and is indicated for the relief of moderate-to-severe pain; the recommended dosing is two capsules every four hours as needed for pain. The national average drug acquisition cost (NADAC) of the generic formulation is $2.74 per capsule.
- **February 2017:** ConZip® (tramadol ER capsules) was updated on the national drug data file (NDDF). ConZip® is supplied as 100mg, 200mg, and 300mg ER oral capsules and is indicated for the treatment of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The capsule formulation is considered biphasic by combining 25% IR tramadol and 75% ER tramadol in one dose; the recommended dosing is one capsule by mouth once daily. ConZip® is available in a generic formulation with a wholesale acquisition cost (WAC) of $7.65 per 100mg capsule. The ER tablet formulation of tramadol is also available as a generic formulation with a NADAC of $1.71 per 100mg tablet.
- **June 2017:** Teva pharmaceuticals introduced an authorized generic of Butrans® (buprenorphine transdermal system). The generic formulation will be available in 5mcg-, 10mcg-, 15mcg-, and 20mcg/hour strengths, but will not be available in the 7.5mcg/hour strength.

Guideline Recommendation(s):

- **February 2017:** The American College of Physicians (ACP) released guidelines recommending that prescribers avoid opioids when treating acute low back pain. The ACP recommends non-drug therapies for initial low back pain treatment including superficial heat, massage, exercise, acupuncture, mindfulness-based stress reduction, tai chi, yoga, cognitive behavioral therapy, or spinal manipulation. If nonpharmacological approaches fail, nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants are recommended followed by tramadol or duloxetine. The ACP considers opioids as a last-line option due to the risk of addiction.
- **June 2017:** The Federation of State Medical Boards (FSMB) updated its guidelines on opioid use for chronic pain. The new polices are intended to underscore the need for physicians to be proactive in curbing the opioid epidemic. Updated recommendations included the following: mental health disorders and depression screening as a part of the initial

evaluation, treatment agreements outlining patient and prescriber responsibilities, using the state prescription drug monitoring programs, avoidance of concomitant benzodiazepine therapy, and physician training before methadone prescribing.

FDA Update(s):

- **April 2017:** The FDA issued a Drug Safety Communication regarding the use of codeine pain and cough medicines or tramadol in children and breastfeeding women. The FDA required several changes to the labels of all prescription medications containing codeine or tramadol. The label changes include the following:
    - Codeine and tramadol are now contraindicated for use in children younger than 12 years of age due to the risk of slowed or difficult breathing.
    - Tramadol is now contraindicated in children under the age of 18 years when used to treat pain following surgery to remove the tonsils and/or adenoids.
    - Codeine or tramadol are not recommended in breastfeeding mothers due to the risk of excess sleepiness, difficulty breastfeeding, or serious breathing problems in the breastfed infant.
    - During calendar year 2016, a total of 7,507 SoonerCare members 12 years of age and younger utilized tramadol or codeine products. May of 2017 saw a 45.80% drop in claims for tramadol and codeine products in members 12 years of age and younger compared to May of 2016.
- **June 2017:** The FDA has asked Endo Pharmaceuticals, the manufacturer of Opana® ER (oxymorphone ER), to remove the product from the market, stating the "benefits of the drug may no longer outweigh its risks". This is the first time the FDA has recommended removal of currently marketed opioid pain medication from sale due to the public health consequences of abuse. The FDA stated that they based their decision on postmarketing data indicating a shift in the route of abuse of Opana® ER from nasal to injection following a reformulation of the product. Injection abuse of Opana® ER has been linked to an outbreak of HIV and hepatitis C.
- **June 2017:** The FDA announced an upcoming workshop in July 2017 to evaluate the impact of abuse-deterrent formulations of opioid analgesics. The FDA Commissioner, Scott Gottlieb, relayed that the meeting is intended to evaluate the real-world data on abuse-deterrent formulations and their efficacy in hindrance of abuse.

News:

- **September 2016:** The Institute for Clinical and Economic Review (ICER) released a draft scoping report stating plans to review the clinical effectiveness and value of abuse-deterrent opioid formulations. The report is intended to evaluate evidence not typically captured in clinical trials including public health effects, reduction in disparities, innovation, and patient experience. The final version of the report is expected to be released July 20, 2017.
- **February 2017:** The American Academy of Pediatrics (AAP) released a policy statement urging a public health approach for women who use opioids during pregnancy rather than a punitive approach. The AAP recommended bolstering efforts targeted at primary prevention like prescription drug monitoring programs and improving access to contraceptives, prenatal care, and treatment for substance use disorder.

Pipeline:

- **August 2016:** Indivior announced positive Phase 3 results for RBP-6000, a monthly depot formulation of buprenorphine, in the treatment of opioid use disorder. Monthly subcutaneous (SC) injections of RBP-6000 over a six-month dosing period demonstrated statistical significance compared to placebo by evaluating urine samples negative for opioids.
- **September 2016:** Grüenthal's cebranopadol, a novel analgesic that acts as a nociceptin/orphanin FQ peptide (NOP) receptor and opioid receptor agonist, demonstrated statistical significance for non-inferiority to morphine sulfate ER in the average amount of daily rescue medication intake in a Phase 3 trial of patients with cancer-related pain.
- **November 2016:** Braeburn Pharmaceuticals announced positive Phase 3 results for CAM2038, a weekly and monthly buprenorphine injection. CAM2038 demonstrated non-inferiority to sublingual buprenorphine in percentage of negative urine samples for opioids.
- **March 2017:** Nektar Therapeutics announced positive results from a Phase 3 trial of NKTR-181, a novel mu-opioid agonist designed to provide pain relief without euphoria. NKTR-181 demonstrated significantly improved chronic back pain relief compared to placebo in opioid naïve patients. NKTR-181 has also demonstrated significantly lower abuse potential than oxycodone in an abuse potential study. The FDA has granted NKTR-181 Fast Track designation for the treatment of moderate-to-severe chronic pain.

Arymo™ ER (Morphine Sulfate Extended-Release Tablets) Product Summary[23]

Indication(s): Arymo™ ER (morphine sulfate ER tablets) is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Dosing:

- Arymo™ ER is available as extended-release oral tablets in the following strengths: 15mg, 30mg, and 60mg.
- Arymo™ ER is administered orally every 8 or 12 hours.
- Patients should be instructed to swallow Arymo™ ER tablets whole. Cutting, breaking, crushing, chewing, or dissolving Arymo™ ER tablets will result in uncontrolled delivery of morphine that could lead to overdose and death.

Boxed Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Efficacy: The efficacy of Arymo™ ER is based on clinical studies of morphine. No clinical studies are provided in the Arymo™ ER prescribing information.

Abuse Deterrence Studies: Arymo™ ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.

- In Vitro Testing: In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the extended-release properties. The results of this testing demonstrated that Arymo™ ER tablets, in comparison to morphine sulfate ER tablets, have increased resistance to cutting, crushing, grinding or breaking using

a variety of tools. When subjected to a liquid environment, the manipulated Arymo™ ER tablets form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

- Oral Pharmacokinetic Study: The pharmacokinetic profile of manipulated and intact Arymo™ ER compared to crushed morphine sulfate ER was evaluated in 38 subjects following oral administration. The study was conducted in a randomized cross-over design. The results demonstrate that oral ingestion of manipulated Arymo™ ER resulted in a higher Cmax, but similar area under the curve (AUC), when compared to intact Arymo™ ER. In addition, manipulated Arymo™ ER had a lower Cmax and longer Tmax than crushed morphine sulfate ER tablets.
- Oral Clinical Abuse Potential Study: An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users. Treatment arms included manipulated Arymo™ ER 60mg tablets, intact Arymo™ ER 60mg tablets, crushed 60mg morphine sulfate ER tablets, and placebo. The study demonstrated that the oral administration of manipulated Arymo™ ER resulted in a statistically lower mean "Drug Liking" score than the oral administration of crushed morphine sulfate ER tablets. However, the difference between manipulated Arymo™ ER and crushed morphine sulfate ER tablets for "Take Drug Again" was not statistically significant, indicating that the difference in "Drug Liking" scores was not clinically meaningful.

Cost Comparison:

Medication	Cost per Unit	Cost per 30 Days
Arymo™ ER (morphine sulfate ER tablets) 30mg	**$8.65**	**$519.00**
morphine sulfate ER tablets 30mg	$0.52	$31.20
morphine sulfate ER capsules 30mg	$3.50	$210.00
MorphaBond™ (morphine sulfate ER tablets) 30mg	$10.80	$648.00

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.
Cost based on a dosing regimen of 30mg twice daily.
Unit = tablet or capsule

Troxyca® ER (Oxycodone/Naltrexone Extended-Release Capsules) Product Summary[24]

Indication(s): Troxyca® ER (morphine/naltrexone ER capsules) is a combination opioid agonist/opioid antagonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Dosing:

- Troxyca® ER is supplied as extended-release oral capsules in the following strengths (oxycodone/naltrexone): 10mg/1.2mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60mg/7.2mg, and 80mg/9.6mg.
- Troxyca® ER is administered orally every 12 hours. There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.
- Patients should be instructed to swallow Troxyca® ER capsules whole. Crushing, chewing, or dissolving the pellets in Troxyca® ER capsules will result in uncontrolled delivery of oxycodone and can lead to overdose or death. Patients who are unable to swallow

Troxyca® ER capsules can sprinkle the capsule contents on applesauce and immediately swallow without chewing. Troxyca® ER pellets should not be administered through a nasogastric or gastric tube.

Boxed Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; Cytochrome (CY) P450 3A4 Interaction; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Efficacy: The analgesic efficacy of Troxyca® ER was evaluated in one randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe chronic low back pain. A higher percentage of subjects receiving Troxyca® ER, compared to placebo, had a ≥ 30% decrease in their weekly average pain intensity scores from baseline to weeks 11 and 12 of the double-blind treatment period (58% versus 44%), while 40% of subjects receiving Troxyca® ER and 30% of subjects receiving placebo had a 50% decrease.

Abuse Deterrence Studies: Troxyca® ER is formulated with a sequestered opioid antagonist, naltrexone, which is released with manipulation by crushing.

- In Vitro Testing: In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When Troxyca® ER is crushed and mixed in a variety of solvents, both oxycodone and naltrexone are simultaneously extracted.
- Oral Abuse Potential Study: A total of 31 non-dependent, recreational opioid abusers evaluated "Drug Liking" via the oral route. Oral administration of crushed 40mg/4.8mg and 60mg/7.2mg Troxyca® ER was associated with statistically significantly lower means and medians for "Drug Liking" compared with crushed 40mg and 60mg IR oxycodone. A total of 74% (23) and 77% (24) experienced some reduction in "Drug Liking" with crushed 40mg/4.8mg Troxyca® ER and crushed 60mg/7.2mg Troxyca® ER compared to crushed IR oxycodone. With crushed 40mg/4.8mg Troxyca® ER, 65% (20) of subjects had at least a 30% reduction and 55% (17) of subjects had at least a 50% reduction in "Drug Liking" compared to crushed 40mg IR oxycodone.
- Intranasal Abuse Potential Study: A total of 27 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids evaluated "Drug Liking" and "Take Drug Again" via the intranasal route. Intranasal administration of crushed Troxyca® ER was associated with statistically significantly lower means and medians for "Drug Liking" and "Take Drug Again" compared with crushed IR oxycodone; 93% (25) experienced at least a 30% reduction in "Drug Liking" with crushed Troxyca® ER compared to crushed IR oxycodone.
- Simulated IV Abuse Potential Study: A total of 29 non-dependent recreational opioid abusers evaluated "Drug Liking" via the intravenous (IV) route. IV administration of the combination of oxycodone and naltrexone was associated with statistically significantly lower mean and median "Drug Liking" and "Take Drug Again" scores compared with oxycodone alone; 90% (26) experienced some reduction in "Drug Liking" with simulated parenteral use of crushed Troxyca® ER compared to IV oxycodone.

Cost Comparison:

Medication	Cost per Unit	Cost per 30 Days
Troxyca® ER (oxycodone/naltrexone ER capsules) 30mg	**Not Available**	**Not Available**
OxyContin® (oxycodone ER tablets) 30mg	$8.36	$501.60*
oxycodone ER tablets 30mg	$6.12	$367.20
Xtampza® ER (oxycodone ER capsules) 27mg	$8.77	$526.20

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.
*Supplementally rebated product.
Cost based on a dosing regimen of 30mg oxycodone base twice daily.
Unit = tablet or capsule

Vantrela™ ER (Hydrocodone Extended-Release Tablets) Product Summary[25]

Indication(s): Vantrela™ ER (hydrocodone ER tablets) is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Dosing:

- Vantrela™ ER is supplied as extended-release oral tablets in the following strengths: 15mg, 30mg, 45mg, 60mg, and 90mg.
- Vantrela™ ER is administered orally every 12 hours. A dose of 90mg every 12 hours (180mg per day) should not be exceeded, as higher doses have not been studied with regard to the effects of hydrocodone on the QT interval.
- Patients should be instructed to swallow Vantrela™ ER tablets whole. Crushing, chewing, or dissolving Vantrela™ ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death.

Boxed Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; CYP450 3A4 Interaction; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Efficacy: The efficacy and safety of Vantrela™ ER were evaluated in a randomized double-blind, placebo-controlled, multi-center clinical trial in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain who required continuous opioid treatment for an extended period of time. Vantrela™ ER provided greater relief of low back pain than placebo as measured by the weekly average of daily worst pain intensity (WPI) scores ($p<0.001$). The proportion of patients who had up to 30% reduction in their average WPI was higher for the Vantrela™ ER treatment group compared to the placebo treatment (57% vs 45%).

Abuse Deterrence Studies: Vantrela™ ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

- In Vitro Testing: In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the ER formulation. Results support that Vantrela™ ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some ER properties despite manipulation. When

Vantrela™ ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.

- Oral Pharmacokinetic Data: Vantrela™ ER tablets were crushed prior to oral administration in non-dependent recreational opioid users and the pharmacokinetics were compared to intact Vantrela™ ER tablets and an IR hydrocodone powder. The results demonstrated that crushing Vantrela™ ER tablets prior to administration increased the maximum observed plasma concentration (Cmax) but not the total exposure (AUC) relative to dosing the intact product. Relative to IR hydrocodone, the Cmax for all Vantrela™ ER treatments was significantly lower and the Tmax significantly longer, consistent with an ER profile.
- Oral Abuse Potential Study: A total of 35 non-dependent opioid abusers evaluated "Drug Liking" via the oral route. The oral administration of crushed Vantrela™ ER was associated with statistically significantly lower mean scores for "Drug Liking" and "Take Drug Again" ($p<0.001$ for both), compared with powdered hydrocodone.
- Intranasal Abuse Potential Study: A total of 34 non-dependent opioid abusers evaluated "Drug Liking" via the intranasal route. The intranasal administration of finely milled Vantrela™ ER was associated with statistically significantly lower mean and median scores for "Drug Liking" and "Take Drug Again" ($p<0.001$ for both), compared with powdered hydrocodone administered intranasally.

Cost Comparison:

Medication	Daily Dosing	Cost per Unit	Cost per 30 Days
Vantrela™ ER (hydrocodone ER tablets) 30mg	**Q 12 Hours**	**Not Available**	**Not Available**
Hysingla® ER (hydrocodone ER tablets) 60mg	Q 24 hours	$21.45	$643.50*
Zohydro® ER (hydrocodone ER capsules) 30mg	Q 12 hours	$8.62	$517.20

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.
*Supplementally rebated product.
Cost based on a dosing regimen of 30mg twice daily or 60mg once daily for Hysingla® ER.
Unit = tablet or capsule, Q = every

Oxaydo® (Oxycodone Immediate-Release Tablets) Product Summary[26]

Indication(s): Oxaydo® (oxycodone tablets) is indicated for the management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Dosing:

- Oxaydo® is supplied as immediate-release oral tablets in the following strengths: 5mg and 7.5mg.
- Oxaydo® is administered orally every 4 to 6 hours. Treatment is recommended to be initiated at a dose of 5mg to 15mg every 4 to 6 hours and titrated to a dose that provides adequate analgesia and minimizes adverse reactions.
- Patients should be instructed to swallow Oxaydo® tablets whole. Oxaydo® is not amenable to crushing and dissolution and should not be administered via nasogastric, gastric, or other feeding tubes as it may cause obstruction of feeding tubes.

Boxed Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; CYP450 3A4 Interaction; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Efficacy: The efficacy of Oxaydo® is based on clinical studies of oxycodone. No clinical studies are provided in the Oxaydo® prescribing information.

Abuse Deterrence Studies: Intranasal "Drug Liking" of Oxaydo® tablets was evaluated in 40 non-dependent recreational opioid users. Crushed Oxaydo® tablets were compared with crushed IR oxycodone tablets in a double-blind, active-comparator, crossover study. Results demonstrated small numeric differences in the median and mean "Drug Liking" scores were lower in response to Oxaydo® than IR oxycodone. A total of 30% of subjects who received Oxaydo® responded that they would "Not Take Drug Again" compared to 5% of subjects who received to IR oxycodone. Study subjects self-administering Oxaydo® reported a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely insufflate two crushed tablets within a fixed time period (21 of 40 subjects). The clinical significance of the difference in "Drug Liking" and difference in response to "Take Drug Again" reported in this study has not yet been established. There is no evidence that Oxaydo® has a reduced abuse liability compared to IR oxycodone**.**

Cost Comparison:

Medication	Cost per Unit	Cost per 30 Days
Oxaydo® (oxycodone tablets) 5mg	**$6.08**	**$729.60**
Oxaydo® (oxycodone tablets) 7.5mg	**$9.11**	**$1,093.20**
oxycodone tablets 5mg	$0.10	$12.00
oxycodone tablets 10mg	$0.17	$20.40

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.
Cost based on a dosing regimen of one tablet every 6 hours.
Unit = tablet

RoxyBond™ (Oxycodone Immediate-Release Tablets) Product Summary[27]

Indication(s): RoxyBond™ (oxycodone IR tablets) is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Dosing:

- RoxyBond™ is supplied as immediate-release oral tablets in the following strengths: 5mg, 15mg, and 30mg.
- RoxyBond™ is administered orally every 4 to 6 hours. Treatment is recommended to be initiated at a dose of 5mg to 15mg every 4 to 6 hours and titrated to a dose that provides adequate analgesia and minimizes adverse reactions.

Boxed Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Ingestion; Neonatal Opioid Withdrawal Syndrome; CYP450 3A4 Interaction; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Efficacy: The efficacy of RoxyBond™ is based on clinical studies of oxycodone. No clinical studies are provided in the RoxyBond™ prescribing information.

Abuse Deterrence Studies: RoxyBond™ is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse even if the tablet is subjected to physical manipulation and/or chemical extraction.

- In Vitro Testing: Laboratory test data demonstrated that, relative to oxycodone IR tablets, RoxyBond™ has increased resistance to cutting, crushing, grinding, or breaking using selected tools. In addition, the intact and manipulated tablets resisted extraction in selected household and laboratory solvents under various conditions. Relative to oxycodone IR tablets, the formulation forms a viscous material that resists passage through a needle; it was also more difficult to prepare solutions suitable for intravenous injection.
- Pharmacokinetic Study: When crushed and insufflated, RoxyBond™ showed a lower peak oxycodone plasma concentration (Cmax ~28% reduction) and a 35% longer time to peak plasma concentration (Tmax) relative to crushed and insufflated oxycodone IR tablets. Similar results were demonstrated when crushed and insufflated RoxyBond™ was compared to intact oral RoxyBond™ with a reduction in Cmax and a longer time to Tmax. Intact oral RoxyBond™ resulted in a Cmax of oxycodone similar to that of crushed and insufflated oxycodone IR, with a similar Tmax.
- Intranasal Abuse Potential Studies: A total of 29 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids evaluated "Drug Liking" and "Take Drug Again" via the intranasal route. Compared to crushed intranasal oxycodone IR tablets, intranasal administration of crushed RoxyBond™ was associated with statistically significantly lower "Drug Liking" and "Take Drug Again" scores. The majority of subjects (86%; n=25) experienced some reduction in "Drug Liking" with crushed intranasal RoxyBond™ compared with crushed intranasal oxycodone IR tablets, whereas 59% (n=17) experienced at least a 30% reduction in "Drug Liking" and 21% (n=6) experienced at least a 50% reduction in "Drug Liking."

Cost Comparison:

Medication	Cost per Unit	Cost per 30 Days
RoxyBond™ (oxycodone tablets) 5mg	**Not Available**	**Not Available**
oxycodone tablets 5mg	$0.10	$12.00

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.
Cost based on a dosing regimen of one tablet every 6 hours.
Unit = tablet

Recommendations

The College of Pharmacy recommends the following:

1. The implementation of an age restriction for all tramadol and codeine products for members younger than 12 years of age. Members younger than 12 years of age would require prior authorization approval for reimbursement of these products. This restriction would include both liquid and solid dosage forms. Authorization would require a patient-specific, clinically significant reason for use of these products despite the medication being contraindicated for the member's age.

2. The movement of Opana® ER (oxymorphone ER) from Tier-3 to the Special Prior Authorization (PA) Tier of the Opioid Analgesics Product Based Prior Authorization (PBPA) category based on FDA recommendations to remove the medication from the market. Authorization would require a patient-specific, clinically significant reason why the member could not use any other available extended-release opioid analgesic.
3. The placement of ConZip® (tramadol ER capsules) into the Special PA Tier of the Opioid Analgesics PBPA category based on net cost. Authorization would require a patient-specific, clinically significant reason why the member could not use the extended-release tablet formulation.
4. The placement of Oxaydo® (oxycodone), RoxyBond™ (oxycodone), and Trezix® (dihydrocodeine/APAP/caffeine) into Tier-3 of the Opioid Analgesics PBPA category. Current short-acting Tier-3 criteria would apply.
5. The placement of Arymo™ ER (morphine sulfate ER), Troxyca® ER (morphine/naltrexone ER), and Vantrela™ ER (hydrocodone ER) into Tier-3 of the Opioid Analgesics PBPA category. Current long-acting Tier-3 criteria would apply.

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

APAP = Acetaminophen, ASA = Aspirin, IR = Immediate-Release, ER = Extended-Release, IBU = Ibuprofen, Cod = Codeine, Caff = Caffeine

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

◊Brand name preferred.

+Brand name Opana® ER preferred. Generic oxymorphone ER tablets require special authorization as they are not abuse-deterrent.

Utilization Details of Opioid Analgesics: Calendar Year 2016

Short-Acting Opioid Analgesics

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
IMMEDIATE-RELEASE HYDROCODONE PRODUCTS					
HYDROCO/APAP TAB 10-325MG	80,180	16,092	$1,692,439.43	4.98	$21.11
HYDROCO/APAP TAB 7.5-325MG	64,634	30,913	$862,887.50	2.09	$13.35
HYDROCO/APAP TAB 5-325MG	41,983	28,463	$357,303.79	1.48	$8.51
HYDROCO/APAP SOL 7.5-325MG	9,203	8,364	$400,255.26	1.1	$43.49
HYDROCOD/IBU TAB 7.5-200MG	1,262	536	$30,013.07	2.35	$23.78
HYDROCOD/IBU TAB 10-200MG	190	36	$69,607.59	5.28	$366.36
IBUDONE TAB 10-200MG	57	18	$5,937.09	3.17	$104.16
XYLON TAB 10-200MG	51	21	$16,710.86	2.43	$327.66
HYDROCOD/IBU TAB 5-200MG	15	10	$1,449.59	1.5	$96.64
HYDROCO/APAP TAB 2.5-325MG	10	9	$158.95	1.11	$15.90
IBUDONE TAB 5-200MG	7	2	$392.98	3.5	$56.14
LORTAB ELX 10-300MG	2	2	$93.45	1	$46.73
HYDROCO/APAP TAB 7.5-500MG	1	1	$0.52	1	$0.52
HYDROCO/APAP TAB 7.5-300MG	1	1	$34.01	1	$34.01
SUBTOTAL	**197,596**	**72,098**	**$3,437,284.09**	**2.74**	**$17.40**
IMMEDIATE-RELEASE OXYCODONE PRODUCTS					
OXYCOD/APAP TAB 10-325MG	24,344	5,934	$1,382,248.64	4.1	$56.78
OXYCOD/APAP TAB 5-325MG	20,251	16,115	$185,955.60	1.26	$9.18
OXYCOD/APAP TAB 7.5-325MG	12,026	5,467	$431,293.00	2.2	$35.86
OXYCODONE TAB 30MG	8,154	1,251	$372,404.21	6.52	$45.67
OXYCODONE TAB 15MG	7,547	1,511	$170,833.81	4.99	$22.64
OXYCODONE TAB 10MG	5,700	1,530	$111,042.50	3.73	$19.48
OXYCODONE TAB 20MG	3,441	710	$123,216.54	4.85	$35.81
OXYCODONE TAB 5MG	2,412	1,203	$26,074.68	2	$10.81
ENDOCET TAB 10-325MG	614	171	$40,320.95	3.59	$65.67
OXYCODONE SOL 5MG/5ML	225	190	$9,528.31	1.18	$42.35
ENDOCET TAB 5-325MG	91	78	$850.47	1.17	$9.35
OXYCODONE CAP 5MG	82	62	$5,965.88	1.32	$72.75
ENDOCET TAB 7.5-325MG	65	38	$2,850.02	1.71	$43.85
OXYCOD/ASA TAB 4.8355-325MG	46	38	$1,554.36	1.21	$33.79
OXYCODONE CON 100/5ML	32	16	$12,328.36	2	$385.26
OXYCODONE CON 20MG/ML	7	4	$5,028.04	1.75	$718.29
OXYCOD/APAP TAB 2.5-325MG	6	6	$730.50	1	$121.75
ENDOCET TAB 2.5-325MG	1	1	$37.52	1	$37.52
SUBTOTAL	**85,044**	**28,925**	**$2,882,263.39**	**2.94**	**$33.89**
CODEINE PRODUCTS					
APAP/CODEINE TAB 300-30MG	20,992	15,154	$161,706.39	1.39	$7.70
APAP/CODEINE TAB 300-60MG	8,396	2,836	$194,605.28	2.96	$23.18
APAP/CODEINE SOL 120-12/5ML	7,588	6,902	$44,169.47	1.1	$5.82
BUT/ASA/CAF/COD CAP 30MG	243	83	$26,647.98	2.93	$109.66
ASCOMP/COD CAP 30MG	124	44	$12,306.53	2.82	$99.25
APAP/CODEINE TAB 300-15MG	121	106	$1,079.89	1.14	$8.92
CODEINE SULF TAB 30MG	26	9	$1,238.50	2.89	$47.63
CODEINE SULF TAB 60MG	7	3	$416.64	2.33	$59.52
CODEINE SULF TAB 15MG	3	3	$43.68	1	$14.56

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
DIHYDROCOD/ASA/CAFF CAP 356-30-16MG	1	1	$101.14	1	$101.14
SYNALGOS-DC CAP 356-30-16MG	1	1	$108.13	1	$108.13
SUBTOTAL	**37,502**	**24,363**	**$442,423.63**	**1.54**	**$11.80**
IMMEDIATE-RELEASE HYDROMORPHONE PRODUCTS					
HYDROMORPHON TAB 4MG	1,261	359	$14,927.58	3.51	$11.84
HYDROMORPHON TAB 2MG	539	348	$4,514.67	1.55	$8.38
HYDROMORPHON TAB 8MG	509	92	$23,372.45	5.53	$45.92
HYDROMORPHON LIQ 1MG/ML	32	10	$3,364.07	3.2	$105.13
DILAUDID TAB 8MG	19	2	$11,134.14	9.5	$586.01
DILAUDID TAB 4MG	2	1	$164.26	2	$82.13
HYDROMORPHON INJ 500/50ML	1	1	$768.23	1	$768.23
SUBTOTAL	**2,363**	**733**	**$58,245.40**	**3.22**	**$24.65**
IMMEDIATE-RELEASE MORPHINE PRODUCTS					
MORPHINE SUL TAB 15MG	2,572	638	$41,662.17	4.03	$16.20
MORPHINE SUL TAB 30MG	865	175	$18,039.03	4.94	$20.85
MORPHINE SUL SOL 100/5ML	115	64	$5,176.05	1.8	$45.01
MORPHINE SUL SOL 10MG/5ML	48	27	$812.84	1.78	$16.93
MORPHINE SUL SOL 20MG/5ML	16	10	$445.17	1.6	$27.82
MORPHINE SUL INJ 10MG/ML	5	5	$24.41	1	$4.88
MORPHINE SUL INJ 10MG/ML	1	1	$23.45	1	$23.45
MORPHINE SUL SUP 10MG	1	1	$221.36	1	$221.36
SUBTOTAL	**3,623**	**854**	**$66,404.48**	**4.24**	**$18.33**
IMMEDIATE-RELEASE TRAMADOL PRODUCTS					
TRAMADOL HCL TAB 50MG	46,048	18,366	$249,478.39	2.51	$5.42
TRAMADL/APAP TAB 37.5-325MG	802	552	$11,608.57	1.45	$14.47
SUBTOTAL	**46,850**	**18,801**	**$261,086.96**	**2.49**	**$5.57**
IMMEDIATE-RELEASE TAPENTADOL PRODUCTS					
NUCYNTA TAB 50MG	65	33	$27,070.63	1.97	$416.47
NUCYNTA TAB 100MG	62	15	$35,033.36	4.13	$565.05
NUCYNTA TAB 75MG	5	4	$2,265.18	1.25	$453.04
SUBTOTAL	**132**	**46**	**$64,369.17**	**2.87**	**$487.65**
IMMEDIATE-RELEASE OXYMORPHONE PRODUCTS					
OXYMORPHONE TAB HCL 10MG	390	57	$99,209.25	6.84	$254.38
OXYMORPHONE TAB HCL 5MG	68	19	$11,084.05	3.58	$163.00
SUBTOTAL	**458**	**73**	**$110,293.30**	**6.27**	**$240.82**
IMMEDIATE-RELEASE FENTANYL PRODUCTS					
FENTANYL CIT INJ 100MCG	32	12	$178.19	2.67	$5.57
SUBSYS SPR 200MCG	8	3	$56,680.48	2.67	$7,085.06
SUBSYS SPR 100MCG	5	5	$11,832.08	1	$2,366.42
SUBSYS SPR 400MCG	5	2	$59,316.90	2.5	$11,863.38
FENTANYL OT LOZ 600MCG	3	1	$4,836.26	3	$1,612.09
SUBSYS SPR 800MCG	1	1	$19,708.82	1	$19,708.82
FENTORA TAB 200MCG	1	1	$143.98	1	$143.98
SUBTOTAL	**55**	**19**	**$152,696.71**	**2.89**	**$2,776.30**
PENTAZOCINE PRODUCTS					
PENTAZ/NALOX TAB 50-0.5MG	977	496	$151,919.21	1.97	$155.50
SUBTOTAL	**977**	**496**	**$151,919.21**	**1.97**	**$155.50**
MEPERIDINE PRODUCTS					
MEPERIDINE TAB 50MG	612	442	$14,030.20	1.38	$22.93
MEPERIDINE SOL 50MG/5ML	560	435	$2,914.25	1.29	$5.20

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
MEPERIDINE TAB 100MG	70	19	$3,529.72	3.68	$50.42
DEMEROL INJ 100MG/ML	1	1	$10.42	1	$10.42
MEPERIDINE INJ 50MG/ML	1	1	$6.24	1	$6.24
DEMEROL INJ 50MG/ML	1	1	$7.97	1	$7.97
SUBTOTAL	**1,245**	**894**	**$20,498.80**	**1.39**	**$16.46**
TOTAL	**375,845**	**116,019***	**$7,647,485.14**	**3.24**	**$20.35**

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

Long-Acting Opioid Analgesics

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
EXTENDED-RELEASE HYDROCODONE PRODUCTS					
HYSINGLA ER TAB 40MG	667	217	$293,186.62	3.07	$439.56
HYSINGLA ER TAB 20MG	625	266	$139,067.53	2.35	$222.51
HYSINGLA ER TAB 30MG	611	229	$200,473.90	2.67	$328.11
HYSINGLA ER TAB 60MG	262	89	$159,600.23	2.94	$609.16
HYSINGLA ER TAB 80MG	133	30	$109,980.51	4.43	$826.92
HYSINGLA ER TAB 100MG	32	7	$34,004.46	4.57	$1,062.64
HYSINGLA ER TAB 120MG	26	6	$29,709.69	4.33	$1,142.68
ZOHYDRO ER CAP 40MG	6	1	$2,769.59	6	$461.60
ZOHYDRO ER CAP 20MG	3	2	$1,513.03	1.5	$504.34
ZOHYDRO ER CAP 10MG	2	1	$915.14	2	$457.57
SUBTOTAL	**2,367**	**633**	**$971,220.70**	**3.74**	**$410.32**
EXTENDED-RELEASE OXYCODONE PRODUCTS					
OXYCONTIN TAB 20MG CR	2,957	759	$995,692.30	3.9	$336.72
OXYCONTIN TAB 30MG CR	1,883	412	$912,377.83	4.57	$484.53
OXYCONTIN TAB 10MG CR	1,860	625	$332,367.36	2.98	$178.69
OXYCONTIN TAB 40MG CR	1,458	301	$880,091.18	4.84	$603.63
OXYCONTIN TAB 15MG CR	1,221	344	$326,155.70	3.55	$267.12
OXYCONTIN TAB 80MG CR	1,124	160	$1,438,400.78	7.03	$1,279.72
OXYCONTIN TAB 60MG CR	949	178	$824,898.79	5.33	$869.23
OXYCODONE TAB 20MG ER	572	221	$151,042.63	2.59	$264.06
OXYCODONE TAB 10MG ER	347	157	$49,303.25	2.21	$142.08
OXYCODONE TAB 40MG ER	314	114	$145,509.27	2.75	$463.41
OXYCODONE TAB 80MG ER	284	69	$257,416.38	4.12	$906.40
OXYCODONE TAB 30MG ER	33	17	$11,936.88	1.94	$361.72
OXYCODONE TAB 15MG ER	17	10	$4,192.41	1.7	$246.61
OXYCODONE TAB 60MG ER	17	7	$12,777.31	2.43	$751.61
SUBTOTAL	**13,036**	**2,182**	**$6,342,162.07**	**5.97**	**$486.51**
EXTENDED-RELEASE HYDROMORPHONE PRODUCTS					
HYDROMORPHON TAB 16MG ER	32	9	$29,920.39	3.56	$935.01
HYDROMORPHON TAB 12MG ER	22	6	$9,718.00	3.67	$441.73
HYDROMORPHON TAB 32MG ER	21	3	$70,107.80	7	$3,338.47
HYDROMORPHON TAB 8MG ER	17	7	$5,321.75	2.43	$313.04
EXALGO TAB 32MG	13	1	$20,827.56	13	$1,602.12
EXALGO TAB 12MG	13	2	$13,857.55	6.5	$1,065.97
SUBTOTAL	**118**	**19**	**$149,753.05**	**6.21**	**$1,269.09**
EXTENDED-RELEASE MORPHINE PRODUCTS					

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
MORPHINE SUL TAB 30MG ER	4,741	841	$248,404.32	5.64	$52.39
MORPHINE SUL TAB 15MG ER	4,423	991	$128,332.95	4.46	$29.01
MORPHINE SUL TAB 60MG ER	2,103	319	$205,808.32	6.59	$97.86
MORPHINE SUL TAB 100MG ER	681	95	$114,281.84	7.17	$167.81
MORPHINE SUL TAB 200MG ER	94	12	$29,238.14	7.83	$311.04
MORPHINE SUL CAP 30MG ER	68	13	$13,248.29	5.23	$194.83
EMBEDA CAP 20-0.8MG	43	12	$10,923.55	3.58	$254.04
MORPHINE SUL CAP 60MG ER	29	5	$12,172.94	5.8	$419.76
MORPHINE SUL CAP 100MG ER	26	5	$18,775.16	5.2	$722.12
MORPHINE SUL CAP 50MG ER	25	4	$5,432.99	6.25	$217.32
MORPHINE SUL CAP 20MG ER	20	4	$4,340.83	5	$217.04
MORPHINE SUL CAP 80MG ER	19	2	$8,018.78	9.5	$422.04
KADIAN CAP 50MG ER	13	1	$11,912.51	13	$916.35
MORPHINE SUL CAP 10MG ER	13	4	$2,331.19	3.25	$179.32
KADIAN CAP 200MG ER	12	1	$46,483.71	12	$3,873.64
MS CONTIN TAB 60MG CR	12	1	$51,794.68	12	$4,316.22
EMBEDA CAP 30-1.2MG	6	4	$2,155.69	1.5	$359.28
EMBEDA CAP 60-2.4MG	3	2	$1,865.27	1.5	$621.76
KADIAN CAP 40MG ER	3	1	$2,477.99	3	$826.00
EMBEDA CAP 50-2MG	2	1	$1,494.64	2	$747.32
SUBTOTAL	**12,336**	**1,924**	**$919,493.79**	**6.41**	**$74.54**
EXTENDED-RELEASE TRAMADOL PRODUCTS					
TRAMADOL HCL TAB 200MG ER	4	1	$382.34	4	$95.59
TRAMADOL HCL TAB 100MG ER	1	1	$61.38	1	$61.38
SUBTOTAL	**5**	**2**	**$443.72**	**2.5**	**$88.74**
EXTENDED-RELEASE TAPENTADOL PRODUCTS					
NUCYNTA ER TAB 250MG	46	6	$53,897.21	7.67	$1,171.68
NUCYNTA ER TAB 200MG	25	7	$22,565.82	3.57	$902.63
NUCYNTA ER TAB 50MG	17	13	$4,561.05	1.31	$268.30
NUCYNTA ER TAB 100MG	13	8	$6,617.46	1.63	$509.04
NUCYNTA ER TAB 150MG	12	4	$8,558.80	3	$713.23
SUBTOTAL	**113**	**28**	**$96,200.34**	**4.04**	**$851.33**
EXTENDED-RELEASE OXYMORPHONE PRODUCTS					
OPANA ER TAB 30MG	154	23	$115,763.37	6.7	$751.71
OPANA ER TAB 20MG	142	24	$74,349.90	5.92	$523.59
OPANA ER TAB 10MG	107	22	$30,298.17	4.86	$283.16
OPANA ER TAB 40MG	99	16	$126,317.03	6.19	$1,275.93
OPANA ER TAB 15MG	39	10	$15,950.39	3.9	$408.98
OPANA ER TAB 7.5MG	4	2	$913.66	2	$228.42
OPANA ER TAB 5MG	4	1	$618.32	4	$154.58
OXYMORPHONE TAB 30MG ER	1	1	$412.43	1	$412.43
SUBTOTAL	**550**	**81**	**$364,623.27**	**6.79**	**$662.95**
EXTENDED-RELEASE FENTANYL PRODUCTS					
FENTANYL DIS 50MCG/HR	1,865	415	$134,386.92	4.49	$72.06
FENTANYL DIS 25MCG/HR	1,649	466	$68,363.55	3.54	$41.46
FENTANYL DIS 100MCG/HR	1,259	192	$173,600.33	6.56	$137.89
FENTANYL DIS 75MCG/HR	1,252	235	$133,959.91	5.33	$107.00
FENTANYL DIS 12MCG/HR	479	171	$67,476.99	2.8	$140.87
FENTANYL DIS 37.5MCG/HR	65	22	$30,386.43	2.95	$467.48
DURAGESIC DIS 100MCG/HR	17	2	$24,041.09	8.5	$1,414.18

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
DURAGESIC DIS 50MCG/HR	12	1	$8,433.12	12	$702.76
SUBTOTAL	**6,598**	**1,100**	**$640,648.34**	**6**	**$97.10**
METHADONE PRODUCTS					
METHADONE TAB 10MG	2,290	319	$46,317.08	7.18	$20.23
METHADONE TAB 5MG	299	88	$5,737.29	3.4	$19.19
METHADONE SOL 5MG/5ML	107	66	$1,412.89	1.62	$13.20
METHADONE SOL 10MG/5ML	9	4	$97.10	2.25	$10.79
METHADOSE CON 10MG/ML	5	2	$151.82	2.5	$30.36
METHADONE CON 10MG/ML	2	2	$42.04	1	$21.02
METHADOSE SF CON 10MG/ML	1	1	$40.77	1	$40.77
DOLOPHINE TAB 10MG	1	1	$19.18	1	$19.18
SUBTOTAL	**2,714**	**443**	**$53,818.17**	**6.13**	**$19.83**
BUPRENORPHINE PAIN PRODUCTS					
BUTRANS DIS 10MCG/HR	872	409	$300,969.47	2.13	$345.15
BUTRANS DIS 15MCG/HR	467	184	$237,825.43	2.54	$509.26
BUTRANS DIS 5MCG/HR	258	143	$59,164.81	1.8	$229.32
BUTRANS DIS 20MCG/HR	255	90	$157,092.63	2.83	$616.05
BUTRANS DIS 7.5/HR	140	51	$44,296.31	2.75	$316.40
BELBUCA MIS 75MCG	10	7	$2,442.20	1.43	$244.22
BELBUCA MIS 150MCG	6	6	$1,633.06	1	$272.18
BELBUCA MIS 600MCG	6	1	$3,687.49	6	$614.58
BELBUCA MIS 300MCG	3	3	$1,066.50	1	$355.50
BELBUCA MIS 450MCG	2	2	$1,155.08	1	$577.54
SUBTOTAL	**2,019**	**667**	**$809,332.98**	**3.03**	**$400.86**
TOTAL	**39,829**	**6,065***	**$10,337,712.10**	**6.57**	**$259.55**

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

Utilization Details of MAT Medications: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBOXONE MIS 8-2MG	6,555	918	$3,024,732.07	7.14	$461.44
NALTREXONE TAB 50MG	2,355	438	$85,377.70	5.38	$36.25
BUPREN/NALOX SUB 8-2MG	2,258	348	$729,709.51	6.49	$323.17
BUPRENORPHIN SUB 8MG	1,237	185	$154,313.71	6.69	$124.75
ZUBSOLV SUB 5.7-1.4	299	85	$129,684.40	3.52	$433.73
SUBOXONE MIS 2-0.5MG	109	30	$22,567.38	3.63	$207.04
VIVITROL INJ 380MG	67	21	$105,219.90	3.19	$1,570.45
BUPRENORPHIN SUB 2MG	51	16	$3,346.39	3.19	$65.62
BUPREN/NALOX SUB 2-0.5MG	45	22	$6,423.79	2.05	$142.75
SUBOXONE MIS 12-3MG	35	10	$23,556.97	3.5	$673.06
SUBOXONE MIS 4-1MG	26	12	$11,140.27	2.17	$428.47
BUNAVAIL MIS 4.2-0.7	25	9	$11,394.96	2.78	$455.80
ZUBSOLV SUB 8.6-2.1	22	5	$15,762.18	4.4	$716.46
BUNAVAIL MIS 6.3-1MG	14	6	$9,631.04	2.33	$687.93
ZUBSOLV SUB 1.4-0.36	10	3	$1,026.54	3.33	$102.65
ZUBSOLV SUB 11.4-2.9	1	1	$471.85	1	$471.85
TOTAL	**13,109**	**1,780***	**$4,334,358.66**	**7.36**	**$330.64**

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

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Appendix O

30-Day Notice to Prior Authorize Brineura™ (Cerliponase Alfa)

Oklahoma Health Care Authority
July 2017

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

Neuronal ceroid lipofucinoses (NCLs), also known as Batten disease, are a group of inherited, neurodegenerative lysosomal storage disorders characterized by progressive deterioration of cognition, motor function impairment, seizures, vision loss, and early death. There are 14 known types of NCLs, which are distinguished by their genetic cause and clinical onset. Each NCL is referred to as a ceroid lipofucinosis (CLN), and then assigned a number to indicate its subtype. Clinical type refers to age of onset and includes infantile (6 to 24 months), late infantile (2 to 3 years), juvenile (5 to 7 years), and adult. NCLs are inherited in an autosomal recessive pattern meaning a child has a 25% chance of inheriting the disease from their carrier parents. NCLs are the most common hereditary progressive neurodegenerative diseases with a prevalence of approximately 1.9 to 9 per million and an incidence of 1.3 to 7 per 100,000 live births (depending on country of family origin). The prevalence of NCL is highest in the Scandinavian countries, particularly Finland. The most prevalent NCLs are CLN3 disease, classic juvenile and CLN2 disease, classic late infantile. CLN2, specifically, has an estimated incidence of approximately 0.5 per 100,000 live births.

CLN2 is caused by mutations in the tripeptidyl-peptidase-1 (TPP-1) gene; TPP-1 mutations lead to reduced TPP-1 enzyme activity and impaired breakdown of peptides in lysosomes, peptide accumulation, and subsequent nerve cell damage. The diagnosis of CLN2 is based on the presence of typical symptoms and reduced activity of TPP-1 enzyme confirmed via an assay of enzymatic activity.

Symptoms of CLN2 disease, classic late infantile, typically appear between the ages of 2 and 4 years starting with delayed language development and epilepsy followed by regression of developmental milestones and myoclonic ataxia. Visual impairment appears at 4 to 6 years of age and rapidly progresses to blindness. Affected children are usually bedridden by 6 years of age and life expectancy ranges from 6 years to early teens.

Motor and language functional abilities for patients with CLN2 disease are assessed via the CLN2 Clinical Rating Scale (CCRS). The CCRS can be used to quantitatively assess disease progression and track loss of function over time. Individually motor and language are evaluated on a scale of 1 to 3 with a score of 3 indicating normal functioning; the highest possible score when assessing both motor and language function is 6.

In April 2017, the U.S. Food and Drug Administration (FDA) approved Brineura™ (cerliponase alfa) to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal CLN2. Cerliponase alfa, the first FDA approved treatment for CLN2, is a recombinant form of TPP-1, serving as an enzyme replacement therapy in TPP-1 deficient

patients. Prior to the approval of cerliponase alfa, the treatment of CLN2 disease was symptomatic and palliative care only. Benzodiazepines have been used to help control seizures and spasticity. Trihexyphenydate may improve dystonia, and patients with swallowing difficulties may benefit from placement of a G-tube.

Market News and Updates[6]

Pipeline:

- There are currently several clinical trials in process that are evaluating different mechanisms to treat NCLs including gene therapy using an adeno-associated viral vector and human central nervous system (CNS) derived stem cell treatment.

Brineura™ (Cerliponase Alfa) Product Summary[7,8]

FDA Approval: April 2017

Indication(s): Brineura™ (cerliponase alfa) is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal CLN2, also known as TPP-1 deficiency.

Dosing:

- Brineura™ is supplied as a 150mg/5mL solution for intraventricular infusion, packaged in cartons containing two single-dose vials along with a 5mL single-dose vial of intraventricular electrolytes injection.
- Brineura™ is also supplied with an administration kit containing syringes, needles, an extension line, an infusion set with micron inline filter, and a port needle.
- Cerliponase alfa and electrolytes injection should be stored in a freezer (-25° to -15°C).
- The recommended dosage of cerliponase alfa is 300mg administered once every other week as an intraventricular infusion followed by an infusion of intraventricular electrolytes over approximately 4.5 hours.
- Cerliponase alfa is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. The intraventricular access device must be implanted prior to the first infusion. It is recommended that the first dose be administered at least 5 to 7 days after device implantation.
- Aseptic technique must be strictly observed during preparation and administration. Cerliponase alfa should be administered by, or under the direction of a physician knowledgeable in intraventricular administration.
- Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.

Mechanism of Action: CLN2 disease is a neurodegenerative disease caused by deficiency of the lysosomal enzyme TPP-1, which catabolizes polypeptides in the CNS. Deficiency in TPP-1 activity results in the accumulation of lysosomal storage materials normally metabolized by this enzyme in the CNS, leading to progressive decline in motor function. Cerliponase alfa is taken up by target cells in the CNS and is translocated to the lysosomes and the activated proteolytic form cleaves tripeptides from the N-terminus of proteins.

Contraindications:

- Acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection)
- Ventriculoperitoneal shunts

Safety:

- Intraventricular Access Device-Related Complications: Cerliponase alfa must be administered using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the intraventricular access device is not compromised prior to each infusion. In case of intraventricular access device complications, the cerliponase alfa infusion should be discontinued. The signs and symptoms of device-related infections may not be apparent, therefore, CSF samples should routinely be sent for testing to detect subclinical device infections. Material degradation of the intraventricular access device reservoir may occur after approximately 105 perforations of the intraventricular access device, equating to approximately 4.3 years of regular administrations.
- Cardiovascular Adverse Reactions: Vital signs (blood pressure, heart rate) should be monitored before each infusion starts, periodically during infusion, and post-infusion in a healthcare setting. Upon completion of the infusion, the patient's status should be clinically assessed and continued observation may be necessary. Electrocardiogram (ECG) monitoring should be performed during the infusion in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In patients without cardiac abnormalities, regular 12-lead ECG evaluations should be performed every six months.
- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in cerliponase alfa-treated patients during clinical studies. A total of 11 (46%) patients experienced hypersensitivity reactions during the infusion or within 24 hours of completion of the infusion. The signs and symptoms observed concomitantly with hypersensitivity reactions included pyrexia, vomiting, pleocytosis, or irritability. Due to the potential for anaphylaxis, appropriate medical support should be readily available when cerliponase alfa is administered. If anaphylaxis occurs, the infusion should be immediately discontinued and appropriate medical treatment initiated. Patients should be observed closely during and after the infusion.

Use in Specific Populations:

- Pregnancy: There are no available data on cerliponase alfa use in pregnant women to inform a drug-associated risk of pregnancy-related outcomes. Animal reproduction studies have not been conducted using cerliponase alfa.
- Lactation: There are no data on the presence of cerliponase alfa in human milk, the effects on the breastfed child, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of cerliponase alfa in patients less than 3 years of age have not been established.

Adverse Reactions: The most common adverse reactions reported in ≥ 8% of symptomatic pediatric patients with CLN2 disease in the cerliponase alfa single-arm clinical study include the following:

- Pyrexia
- ECG abnormalities
- Decreased CSF protein
- Vomiting
- Seizures
- Hypersensitivity
- Increased CSF protein
- Hematoma
- Headache
- Irritability
- Pleocytosis
- Device-related infection
- Bradycardia
- Feeling jittery
- Hypotension

Efficacy: The efficacy of cerliponase alfa was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile CLN2 disease, confirmed by TPP-1 deficiency. Cerliponase alfa-treated patients were compared to untreated patients from a natural history cohort. The motor domain of a CLN2 Clinical Rating Scale (CCRS) was used to assess disease progression. Scores ranged from 3 (grossly normal) to 0 (profoundly impaired) with unit decrements representing milestone events in the loss of motor function (ability to walk or crawl). Due to the inability to establish comparability for the CLN2 language domain ratings between the clinical study and the natural history cohort, efficacy of cerliponase alfa for the language domain cannot be established. A total of 24 patients 3 to 8 years of age were enrolled in the single-arm clinical study. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with cerliponase alfa 300mg every other week for 48 weeks, and continued treatment during the extension period. Patients were assessed for decline in the motor domain of the CCRS at 48, 72, and 96 weeks. Decline was defined as having an unreversed (sustained) 2-category decline or an unreversed score of 0. Patients' responses to cerliponase alfa treatment were evaluated if at screening a combined motor plus language CLN2 score of less than 6 was recorded. Data used in the analyses from the natural history cohort began at 36 months of age or greater and at the first time a motor plus language CLN2 score less than 6 was recorded. Motor scores of the 22 cerliponase alfa-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients. The results of logistic modeling with covariates, demonstrated the odds of cerliponase alfa-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio [95% CI]: 13.1 [1.2, 146.9]).

- In an unadjusted non-randomized comparison of the 22 patients treated with cerliponase alfa at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline in the motor domain of the CCRS. Results from the natural history cohort demonstrated progressive decline in motor function; of the 42 patients in the natural history cohort, 21 (50%) experienced an unreversed (sustained) 2-category decline or unreversed score of 0 in the motor domain of the CCRS.
- To further assess efficacy, the 22 patients from the cerliponase alfa clinical study with a baseline combined motor plus language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. At 96 weeks, the matched analysis based on 17

pairs demonstrated fewer declines in the motor domain for cerliponase alfa-treated patients compared to untreated patients in the natural history cohort.

Time Point	Natural History Cohort (N=17)	Cerliponase Alfa-Treated (N=17)	Difference	Odds Ratio (OR)
	n (%)	n (%)	% (95% CI)	OR (95% CI)
Week 48	13 (76)	16 (94)	18% (-19, 51)	4 (0.4, 200)
Week 72	11 (65)	16 (94)	29% (-7, 61)	5.9 (0.7, 250)
Week 96	6 (35)	16 (94)	59% (24, 83)	11 (1.6, 500)

Additional Studies: The efficacy and safety of cerliponase alfa were also evaluated in a Phase 1/2 open-label, single arm, dose-escalation study. A total of 24 patients were included in the study; these patients were an average of 4.3 years of age, had a mean baseline CLN2 motor/language score of 3.6, had stable seizure control, had not suffered status epilepticus in the four weeks before initiation of treatment, and did not have other inherited neurologic disorders. Efficacy of cerliponase alfa was evaluated by comparing CLN2 disease progression in the treatment group to a historical cohort of 58 patients who had been evaluated throughout the progression of their disease via the Hamburg late-infantile NCL scale (motor, language, seizures, and visual function). Only the motor and language portions of the scale were utilized. An additional secondary endpoint evaluated gray matter volume in the treatment group compared to historical data. Gray matter volume can be used as an indicator of CLN2 disease progression.

- At 48 weeks the percentage of treated subjects who experienced less than 2-point decline on the motor/language CLN2 score was 87% (p=0.0002) and 65% of patients experienced no decline in motor-language CLN2 score (13 no change, 2 improved by one point).
- At 48 weeks the cortical gray matter volume measured by MRI scans was 408.3 cm^3 (vs. baseline 452.0 cm^3). A total of 9.7% of gray matter volume loss occurred in treated patients vs. 14.5% in historically untreated patients. The statistical significance of this was not reported.

Cost:

Product	Cost per Treatment	Cost per Month	Annual Cost
Brineura™ (cerliponase alfa) 300mg	**$18,000.00**	**$36,000.00**	**$468,000.00**

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.

Recommendations

The College of Pharmacy recommends the prior authorization of Brineura™ (cerliponase alfa) with the following criteria:

Brineura™ (Cerliponase Alfa) Approval Criteria:

1. An FDA-approved diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) also known as tripeptidyl peptidase-1 (TPP-1) deficiency; and

2. Member must have confirmed TPP-1 enzymatic deficiency via enzyme assay, confirmed by molecular analysis; and
3. Member must be at least 3 years of age or older; and
4. Brineura™ must be prescribed by a specialist with expertise in treatment of CLN2 (or be an advanced care practitioner with a supervising physician who is a specialist with expertise in treating CLN2); and
5. Brineura™ must be administered in a healthcare facility by a prescriber who is knowledgeable in intraventricular administration; and
6. Member must not have ventriculoperitoneal shunts or acute intraventricular access device-related complications; and
7. Member must not have documented generalized status epilepticus within 4 weeks of initiating treatment; and
8. Prescriber must verify member's blood pressure and heart rate will be monitored prior to each infusion, during infusion, and post-infusion; and
9. Prescriber must be willing to perform regular 12-lead electrocardiogram (ECG) evaluation at baseline and at least every 6 months and verify that they are acceptable to the prescriber; and
10. A baseline assessment must be performed to assess the Motor plus Language CLN2 score; and
11. Initial authorizations will be for the duration of six months, at which time compliance will be required for continued approval. After 12 months of utilization, the prescriber must verify the member is responding to the medication as demonstrated by a two point or less decline in Motor plus Language CLN2 score from baseline; and
12. Approval quantity will be based on Brineura™ prescribing information and FDA approved dosing regimen.

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Appendix P

Calendar Year 2016 Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Marplan® (Isocarboxazid) and Desyrel® (Trazodone 300mg Tablets)

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
citalopram (Celexa®)			fluoxetine 60mg tablets
escitalopram (Lexapro®)			fluoxetine DR (Prozac® Weekly™)
fluoxetine (Prozac®, Sarafem®)			fluvoxamine CR (Luvox CR®)
fluvoxamine (Luvox®)			paroxetine CR (Paxil CR®)
paroxetine (Paxil®)			paroxetine (Pexeva®)
sertraline (Zoloft®)			
Dual-Acting Antidepressants			
bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	vilazodone (Viibryd®)	desvenlafaxine (Khedezla®)	bupropion ER (Aplenzin®)
duloxetine (Cymbalta®)		desvenlafaxine (Pristiq®)	bupropion ER (Forfivo XL®)
mirtazapine (Remeron®, Remeron® SolTab™)		levomilnacipran (Fetzima®)	duloxetine 40mg (Irenka™)
trazodone (Desyrel®)		nefazodone (Serzone®)	trazodone ER (Oleptro®)
venlafaxine (Effexor®, Effexor XR® capsules)			venlafaxine ER tablets (Effexor XR® tablets)
Monoamine Oxidase Inhibitors (MAOIs)			
		phenelzine (Nardil®)	
		selegiline (Emsam®)	
		tranylcypromine (Parnate®)	
Unique Mechanisms of Action			
		vortioxetine (Trintellix®)	

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
CR = Controlled-Release, DR = Delayed-Release, ER = Extended-Release

Antidepressant Tier-2 Approval Criteria:

1. Member must have a documented, recent (within six months) trial of two Tier-1 medications at least four weeks in duration each and titrated to recommended dosing, that did not provide an adequate response. Tier-1 selection must include at least one medication from the SSRI category and one trial with duloxetine; or
2. Prior stabilization on the Tier-2 medication documented within the last 100 days. A past history of success on the Tier-2 medication will also be considered with adequate documentation; or
3. A unique FDA-approved indication not covered by Tier-1 medications or other medications from a different therapeutic class; or
4. A petition may be submitted for consideration whenever a unique patient-specific situation exists.

Antidepressant Tier-3 Approval Criteria:

1. Member must have a documented, recent (within six months) trial with two Tier-1 medications (one medication from the SSRI category and one trial with duloxetine) and a trial of a Tier-2 medication at least four weeks in duration each and titrated to recommended dosing, that did not provide an adequate response; or
2. Prior stabilization on the Tier-3 medication documented within the last 100 days. A past history of success on the Tier-3 medication will also be considered with adequate documentation; or
3. A unique FDA-approved indication not covered by a lowered tiered medication or other medications from a different therapeutic class; or
4. A petition may be submitted for consideration whenever a unique patient-specific situation exists.

Antidepressant Special Prior Authorization (PA) Approval Criteria:

1. Use of any Special PA medication will require a patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 medications; or
2. A petition may be submitted for consideration whenever a unique patient-specific situation exists.
3. Tier structure rules still apply.
4. When Irenka™ (duloxetine 40mg) is being requested for non-depression related diagnoses, the criteria below will apply:
    a. An FDA approved diagnosis of diabetic peripheral neuropathy or chronic musculoskeletal pain; and
    b. A patient-specific, clinically significant reason why the member cannot use two duloxetine 20mg capsules in place of Irenka™ 40mg capsules; and
    c. A quantity limit of 30 capsules per 30 days will apply.

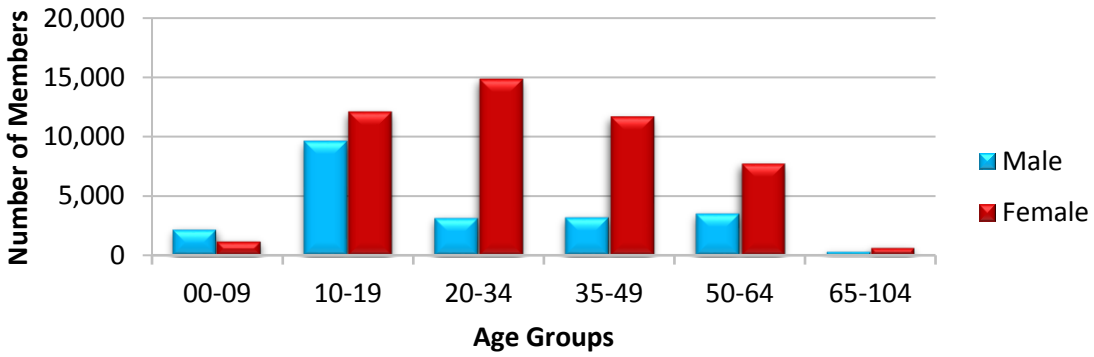
Utilization of Antidepressants: Calendar Year 2016

Comparison of Calendar Years

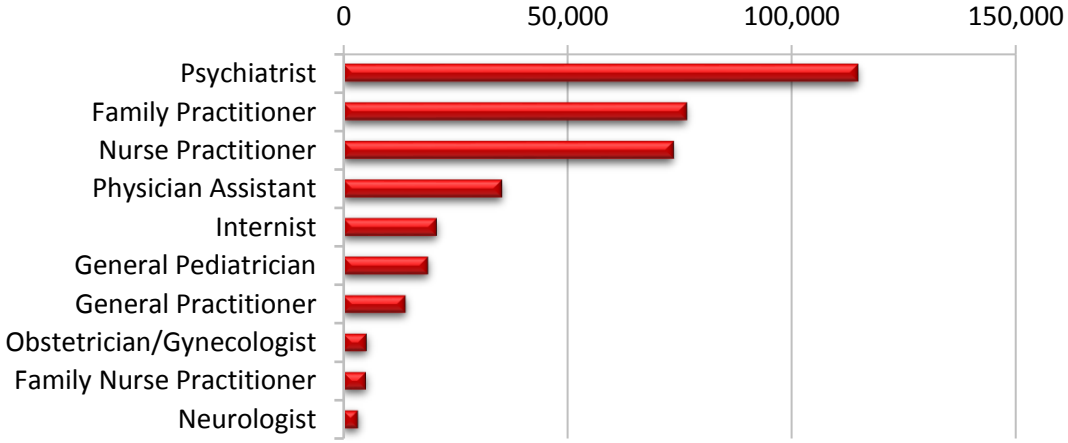
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	66,747	362,781	$4,946,020.47	$13.63	$0.41	13,986,781	12,026,083
2016	69,990	382,520	$5,213,965.72	$13.63	$0.41	14,819,882	12,761,167
% Change	**4.90%**	**5.40%**	**5.40%**	**0.00%**	**0.00%**	**6.00%**	**6.10%**
Change	**3,243**	**19,739**	**$267,945.25**	**$0.00**	**$0.00**	**833,101**	**735,084**

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

Demographics of Members Utilizing Antidepressants

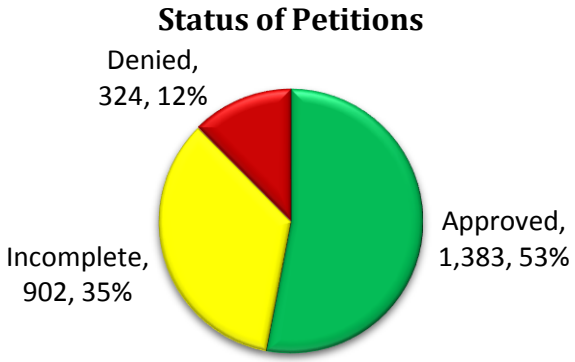


Top Prescriber Specialties of Antidepressants by Number of Claims



Prior Authorization of Antidepressants

There were 2,609 prior authorization requests submitted for antidepressants during calendar year 2016. Computer edits are in place to detect lower tiered medications in the member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.



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

Anticipated Patent Expiration(s):

- Emsam® (selegiline extended-release [ER] transdermal patches): June 2018
- Viibryd® (vilazodone tablets): June 2022
- Pexeva® (paroxetine tablets): May 2025
- Aplenzin® (bupropion ER tablets): June 2026
- Forfivo XL® (bupropion ER tablets): June 2027
- Pristiq® (desvenlafaxine ER tablets): July 2027
- Oleptro® (trazodone ER tablets): March 2029
- Trintellix® (vortioxetine tablets): June 2031
- Fetzima® (levomilnacipran ER capsules): May 2032

News:

- **May 2017:** To help clinicians who treat adults with major depressive episodes (MDE) and mixed features, an international panel of experts on mood disorders convened to develop a consensus guideline on how best to recognize and treat mixed depression. These guidelines were published in Cambridge University's Journal, *CNS Spectrums*. This followed the introduction of a "mixed features" specifier for major depressive disorder (MDD) in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). According to DSM-5, to meet criteria for depression with mixed features, patients must meet threshold criteria for an MDE and subthreshold symptoms of mania or hypomania, or they must have syndromal mania and subthreshold depressive symptoms. The guidelines recommend the following:
    - All patients who receive antidepressants for an MDE be monitored for signs of abnormal behavioral activation or psychomotor acceleration. Monitoring is necessary because the use of antidepressants in patients with MDE who have mixed features may not alleviate depressive symptoms and may pose a potential hazard for exacerbating subthreshold mania symptoms that accompany depression.
    - Consideration should be given to alternative psychotropic agents with demonstrated efficacy in the treatment of depressive symptoms as part of MDE treatment along with an antidepressant medication. Clinicians are encouraged to think about the possibility of mixed features in all patients with depression.

- Clinicians should avoid using antidepressants as first-line treatment for patients with even low levels of mania symptoms mixed with depression.

- **October 2016:** The U.S. Food and Drug Administration (FDA) announced the placement of 27 drugs and drug classes on its watch list based on reports of adverse events from April to June of 2016. This list included the antidepressant product class and the potential risk of stress cardiomyopathy from these medications. The FDA has not concluded that there is a causal relationship, but rather intends to investigate whether one exists. If the study uncovers a link, the FDA could collect more data to better describe the threat, revise the drug's label, or order a Risk Evaluation and Mitigation Strategy. In rare cases, the drug could be pulled from the market.

Pipeline:

- **ALKS 5461:** Alkermes announced the initiation of study 217, a Phase 3b trial of ALKS 5461, a once-daily, oral investigational medicine for the adjunctive treatment of MDD. ALKS 5461 consists of samidorphan and buprenorphine. It is designed to rebalance brain function through endogenous opioid modulation. Study 217 will evaluate the efficacy and safety of ALKS 5461 in patients suffering from MDD who have had an inadequate response to commonly prescribed drugs for depression, including selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Alkermes plans to submit a New Drug Application (NDA) to the FDA for ALKS 5461 by year-end 2017.
- **AXS-05:** Axsome Therapeutics, Inc. is currently evaluating their novel, oral investigational drug, AXS-05. This drug is a combination of bupropion and dextromethorphan being studied for treatment-resistant depression. Axsome's Phase 3 multicenter, randomized, double-blind, active-controlled trial, STRIDE-1, includes patients with MDD who have previously failed one or two antidepressant treatments. The trials consists of an open-label, 6-week lead-in period with bupropion followed by a randomly assigned 1:1 ratio of treatment with bupropion or AXS-05 in a double-blind fashion for those who fail to respond to bupropion during the lead-in period.
- **Brexanolone:** Sage Therapeutics announced in June 2017 that *The Lancet* published results from a Phase 2, double-blind, randomized and placebo-controlled study of brexanolone (SAGE-547) in women with severe postpartum depression (PPD). Brexanolone is an allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors. The study found that treatment with brexanolone (60 hour continuous intravenous [IV] infusion) resulted in a clinically meaningful and statistically significant mean reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score, a common measure of depression severity. Results began at 24 hours and were maintained at similar magnitude until the 30-day follow-up. Brexanolone has been granted Breakthrough Therapy designation by the FDA for the treatment of PPD. Brexanolone is also being developed as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE).
- **Esketamine:** A study published in the journal *Biological Psychiatry* showed that esketamine, a component of the general anesthetic ketamine, showed rapid and significant improvement in depressive symptoms in patients who do not respond to

currently available therapies. In this double-blind study, 30 patients were randomly assigned to receive placebo or a 0.2mg/kg or 0.4mg/kg dose of esketamine. The patients received two IV doses during the double-blind phase, followed by a 2-week follow up phase in which patients could receive up to four additional optional open-label doses. The earliest onset of an antidepressant effect was measured two hours after the first infusion. Within three days, over 60% of patients receiving either dose of esketamine saw improvement in depressive symptoms. None of the patients in the placebo group responded. Clinical trials are underway to test a wider range of doses to determine the optimal dosing, assess other possible side effects, and establish the safety of esketamine in the longer term.

- **Rapastinel:** Allergan announced in January 2016 that its Phase 3 ready investigational medication rapastinel (GLYX-13) received Breakthrough Therapy designation from the FDA for adjunctive treatment of MDD. This followed the Fast Track Designation for rapastinel granted by the FDA in 2014. Rapastinel is an IV formulation of a novel N-methyl-D-aspartate (NMDA) receptor partial agonist. The Breakthrough Therapy designation was based on preclinical and preliminary clinical evidence for rapastinel, which supports a rapid (within one day) and sustained antidepressant effect over the course of the Phase 2 studies.
- **REL-1017:** Relmada Therapeutics, Inc. announced in April 2017 that the FDA granted Fast Track designation for d-Methadone (REL-1017, dextromethadone), the company's novel NMDA receptor antagonist in development for the adjunctive treatment of MDD. As an enantiomer of racemic methadone, REL-1017 has been shown to possess NMDA antagonist properties with virtually no opioid activity at the expected therapeutic doses. Relmada is planning to advance the development program for REL-1017 to a Phase 2a randomized, double-blind, placebo-controlled study in patients with MDD. REL-1017, is also being developed as a rapid-acting, oral agent for the treatment of neuropathic pain and other potential CNS pathological conditions.
- **SAGE-217:** Sage Therapeutics announced in May 2017 that the FDA granted Fast Track Designation to SAGE-217 for development as a potential treatment for MDD. SAGE-217 is a novel, orally-active neuroactive steroid that is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors. It is currently in Phase 2 development for both mood and movement disorders.

Marplan® (Isocarboxazid) Product Summary[11]

Indication(s): Marplan® (isocarboxazid) is indicated for the treatment of depression. Because of its potentially serious side effects, isocarboxazid is not an antidepressant of first choice in the treatment of newly diagnosed depressed patients.

Dosing:

- Isocarboxazid is supplied as a 10mg oral tablet.
- For maximum therapeutic effect, the dosage must be individually adjusted on the basis of careful observation of the patient. Daily dosage should be divided into two to four dosages.
- The recommended initial dose of isocarboxazid is 10mg twice daily.

- If tolerated, the dosage may be increased by increments of 10mg every two to four days to achieve a dosage of 40mg daily by the end of the first week of treatment. The dosage can then be increased by increments of up to 20mg/week, if needed and tolerated.
- The maximum recommended dose is 60mg/day.

Mechanism of Action: Isocarboxazid is a non-selective hydrazine monoamine oxidase inhibitor (MAOI). The mechanism by which MAOIs act as antidepressants is not fully understood, but it is thought to involve the elevation of brain levels of biogenic amines.

Boxed Warning: Suicidality and Antidepressant Drugs

- Antidepressants increase the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies with MDD and other psychiatric disorders.
- The use of isocarboxazid or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 years and older.
- Depression and certain other psychiatric disorders are themselves associated with increased risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised of the need for close observation and communication with the prescriber. Isocarboxazid is not approved for use in pediatric patients.
- Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants.
- The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Contraindications:

- Isocarboxazid should not be administered in combination with any of the following:
  - MAOIs or dibenzazepine derivatives
  - SSRIs
  - Some CNS depressants (including narcotics and alcohol)
  - Antihypertensives
  - Diuretics
  - Antihistamines
  - Sedative or anesthetic drugs
  - Buproprion HCL
  - Buspirone HCL
  - Dextromethorphan
  - Meperidine

- Cheese or other high tyramine content
- Caffeine (excessive quantities)
- Sympathomimetics (including amphetamines)

- Isocarboxazid should not be administered to patients with the following conditions:
  - Hypersensitivity to isocarboxazid
  - Cerebrovascular disorders
  - Pheochromocytoma
  - Liver disease
  - Renal impairment

Warnings and Precautions:

- Hypertensive Crises: The most important reaction associated with MAOIs is the occurrence of hypertensive crises, which can be fatal, resulting from the co-administration of MAOIs and certain drugs and foods (see list above).
- Hypotension: Hypotension has been observed during isocarboxazid therapy. Symptoms of postural hypotension are seen most commonly, but not exclusively, in patients with preexistent hypertension. Blood pressure usually returns rapidly to pretreatment levels upon discontinuation of the drug. Gradual dose increases are recommended in patients showing a tendency toward hypotension at the beginning of therapy.
- Lower Seizure Threshold: Isocarboxazid lowers the convulsive threshold in some animal experiments; therefore, suitable precautions are recommended in epileptic patients. Isocarboxazid has varying effects in epileptic patients, causing increased frequency of seizures in some and decreased frequency in others.
- Patients With Concomitant Illness:
  - MAOIs, like isocarboxazid, can suppress anginal pain that would otherwise serve as a warning of myocardial ischemia.
  - MAOIs, like isocarboxazid, can contribute to hypoglycemic episodes in diabetic patients receiving insulin or glycemic agents. Isocarboxazid should be used with caution in diabetic patients.
  - Isocarboxazid may aggravate coexisting symptoms in depression, such as anxiety and agitation.
  - Isocarboxazid should be used cautiously in hyperactive or agitated patients, as well as in schizophrenic patients, because it may cause excessive stimulation.
  - Isocarboxazid should be used with caution in hyperthyroid patients because of their increased sensitivity to pressor amines.

Adverse Reactions: The most commonly observed adverse events that occurred in patients taking isocarboxazid with an incidence of 5% or greater and at least twice the incidence in placebo include: nausea, dry mouth, and dizziness.

Use in Specific Populations:

- Pregnancy: Isocarboxazid is Pregnancy Category C. Its potential reproductive toxicity has not been adequately evaluated in animals. Isocarboxazid should be given to a pregnant woman only if clearly needed.
- Lactation: Levels of excretion of isocarboxazid and/or its metabolites in human milk have not been determined, and effects on the nursing infant are unknown.

- Pediatric Use: Isocarboxazid is not recommended for use in patients under 16 years of age, as safety and effectiveness in pediatric populations have not been demonstrated.

Efficacy: The effectiveness of isocarboxazid was demonstrated in two 6-week placebo-controlled studies conducted in adult outpatients with depressive symptoms that corresponded to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) category of MDD. Patients were initiated with a dose of 10mg twice daily, with increases every 2 to 4 days, as tolerated, until a therapeutic effect was achieved, up to a maximum dose of 80mg/day. Doses were administered on a divided schedule ranging from 2 to 4 times a day. The mean dose overall for both studies was approximately 40mg/day. In both studies at the end of six weeks, patients receiving isocarboxazid had significantly greater reduction in signs and symptoms of depression evaluated by the Hamilton Depression Scale, for both the Total Score and the Depressed Mood Score, than patients who received placebo.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 30 days
Marplan® (isocarboxazid) 10mg tablet	**$4.31**	**$517.20***
Cymbalta® (duloxetine) 60mg capsule	$0.26	7.80^{\Delta}$
Nardil® (phenelzine) 15mg tablet	$0.48	57.60^{\Delta}$

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 = tablet or capsule
*Cost per 30 days based on 40mg daily dose as caution is indicated in patients for whom a dose of 40mg/day is exceeded.
$^{\Delta}$Cost per 30 days based on typical treatment dose of 60mg daily.

Cost Comparison[12]

There are several strengths of trazodone available for the treatment of MDD. The cost of trazodone 300mg differs greatly from the cost of other strengths of trazodone. The national drug acquisition cost (NADAC) of trazodone 300mg is $2.90 per tablet. This results in a 30-day supply costing $87.00. As shown below a 30-day supply of the other available strengths of trazodone, at an equivalent dose, is significantly less. For example, the cost of two 150mg trazodone tablets (300mg total dose) is $12.00 for a 30 day supply.

Cost Comparison:

Medication	Cost Per Tablet	Cost for 30 Days of Therapy*
Desyrel® 300mg (trazodone tablets)	**$2.90**	**$87.00**
Desyrel® 150mg (trazodone tablets)	$0.20	$12.00
Desyrel® 100mg (trazodone tablets)	$0.09	$8.10
Desyrel® 50mg (trazodone tablets)	$0.05	$9.00

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.
*30 days of therapy based on 300mg/day of trazodone.

Recommendations

The College of Pharmacy recommends the following:

1. The placement of Marplan® (isocarboxazid) into the Special Prior Authorization (PA) Tier of the Antidepressant Product Based Prior Authorization (PBPA) category based on wholesale acquisition cost (WAC). The following criteria will apply:
    a. **Marplan® (Isocarboxazid) Approval Criteria:**
        i. A patient-specific, clinically significant reason why the member cannot use any of the Tier-3 monoamine oxidase inhibitors (MAOIs) or other cost-effective, lower tiered alternatives in place of Marplan®. Tier structure rules still apply.
2. The placement of Desyrel® (trazodone) 300mg into the Special PA Tier of the Antidepressant PBPA category based on NADAC compared to other trazodone strengths. The following criteria will apply:
    a. **Desyrel® (Trazodone 300mg Tablets) Approval Criteria:**
        i. A patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 products including two trazodone 150mg tablets or three trazodone 100mg tablets to achieve a 300mg dose.
3. Move desvenlafaxine (generic Pristiq®) from Tier-3 to Tier-2 based on NADAC. Current Tier-2 criteria will apply.

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
citalopram (Celexa®)			fluoxetine 60mg tablets
escitalopram (Lexapro®)			fluoxetine DR (Prozac® Weekly™)
fluoxetine (Prozac®, Sarafem®)			fluvoxamine CR (Luvox CR®)
fluvoxamine (Luvox®)			paroxetine CR (Paxil CR®)
paroxetine (Paxil®)			paroxetine (Pexeva®)
sertraline (Zoloft®)			
Dual-Acting Antidepressants			
bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	**desvenlafaxine (Pristiq®)**	desvenlafaxine (Khedezla®)	bupropion ER (Aplenzin®)
duloxetine (Cymbalta®)	vilazodone (Viibryd®)	levomilnacipran (Fetzima®)	bupropion ER (Forfivo XL®)
mirtazapine (Remeron®, Remeron® SolTab™)		nefazodone (Serzone®)	duloxetine 40mg (Irenka™)
trazodone (Desyrel®)			**trazodone 300mg tablet (Desyrel®)**
venlafaxine (Effexor®, Effexor XR® capsules)			trazodone ER (Oleptro®)
			venlafaxine ER tablets (Effexor XR® tablets)
Monoamine Oxidase Inhibitors (MAOIs)			
		phenelzine (Nardil®)	**isocarboxazid (Marplan®)**
		selegiline (Emsam®)	
		tranylcypromine (Parnate®)	
Unique Mechanisms of Action			
		vortioxetine (Trintellix®)	

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
CR = Controlled-Release, DR = Delayed-Release, ER = Extended-Release

Utilization Details of Antidepressants: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
TIER-1 MEDICATIONS						
SERTRALINE PRODUCTS						
SERTRALINE TAB 100MG	29,837	6,952	$198,011.90	$0.20	$6.64	3.80%
SERTRALINE TAB 50MG	27,646	9,851	$171,021.67	$0.19	$6.19	3.28%
SERTRALINE TAB 25MG	12,174	4,487	$76,402.45	$0.20	$6.28	1.47%
SERTRALINE CON 20MG/ML	506	143	$31,611.58	$1.92	$62.47	0.61%
ZOLOFT TAB 100MG	7	1	$2,514.64	$12.39	$359.23	0.05%
SUBTOTAL	**70,170**	**21,434**	**$479,562.24**	**$0.21**	**$6.83**	**9.21%**
TRAZODONE PRODUCTS						
TRAZODONE TAB 50MG	27,927	8,320	$137,939.04	$0.16	$4.94	2.65%
TRAZODONE TAB 100MG	20,426	5,670	$128,273.83	$0.19	$6.28	2.46%
TRAZODONE TAB 150MG	12,348	3,099	$119,798.40	$0.30	$9.70	2.30%
TRAZODONE TAB 300MG	265	96	$29,404.86	$3.24	$110.96	0.56%
SUBTOTAL	**60,966**	**17,185**	**$415,416.13**	**$0.21**	**$6.81**	**7.97%**
FLUOXETINE PRODUCTS						
FLUOXETINE CAP 20MG	27,503	8,700	$132,661.08	$0.15	$4.82	2.54%
FLUOXETINE CAP 40MG	14,024	3,759	$123,668.81	$0.26	$8.82	2.37%
FLUOXETINE CAP 10MG	11,559	4,196	$60,033.95	$0.17	$5.19	1.15%
FLUOXETINE TAB 10MG	3,601	1,235	$98,975.81	$0.87	$27.49	1.90%
FLUOXETINE TAB 20MG	2,304	843	$127,121.17	$1.69	$55.17	2.44%
FLUOXETINE SOL 20MG/5ML	1,231	290	$12,171.26	$0.33	$9.89	0.23%
PROZAC CAP 20MG	21	3	$20,135.89	$24.95	$958.85	0.39%
PROZAC CAP 40MG	9	1	$13,265.24	$49.13	$1,473.92	0.25%
SUBTOTAL	**60,252**	**19,027**	**$588,033.21**	**$0.30**	**$9.76**	**11.27%**
CITALOPRAM PRODUCTS						
CITALOPRAM TAB 20MG	19,709	6,802	$91,261.63	$0.13	$4.63	1.75%
CITALOPRAM TAB 40MG	11,207	3,176	$47,675.60	$0.11	$4.25	0.91%
CITALOPRAM TAB 10MG	8,375	2,959	$43,842.99	$0.16	$5.23	0.84%
CITALOPRAM 10MG/5ML	190	43	$7,746.98	$1.38	$40.77	0.15%
SUBTOTAL	**39,481**	**12,980**	**$190,527.20**	**$0.14**	**$4.83**	**3.65%**
ESCITALOPRAM PRODUCTS						
ESCITALOPRAM TAB 10MG	16,224	5,755	$117,833.70	$0.22	$7.26	2.26%
ESCITALOPRAM TAB 20MG	15,868	3,933	$121,369.61	$0.22	$7.65	2.33%
ESCITALOPRAM TAB 5MG	1,904	732	$14,065.53	$0.24	$7.39	0.27%
ESCITALOPRAM 5MG/5ML	194	49	$22,324.60	$4.02	$115.08	0.43%
LEXAPRO TAB 20MG	14	3	$8,341.43	$9.27	$595.82	0.16%
LEXAPRO TAB 10MG	12	3	$3,119.97	$8.67	$260.00	0.06%
SUBTOTAL	**34,216**	**10,475**	**$287,054.84**	**$0.25**	**$8.39**	**5.51%**
BUPROPION PRODUCTS						
BUPROPN TAB 150MG XL	6,905	2,618	$155,482.18	$0.65	$22.52	2.98%
BUPROPN TAB 300MG XL	6,309	1,682	$157,553.10	$0.68	$24.97	3.02%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
BUPROPION TAB 150MG SR	5,549	1,995	$70,701.56	$0.40	$12.74	1.36%
BUPROPION TAB 100MG	2,079	724	$56,616.54	$0.88	$27.23	1.09%
BUPROPION TAB 100MG SR	1,970	808	$25,447.27	$0.42	$12.92	0.49%
BUPROPION TAB 75MG	1,831	685	$37,071.97	$0.66	$20.25	0.71%
BUPROPION TAB 200MG SR	990	260	$22,285.04	$0.72	$22.51	0.43%
BUPROPION TAB 150MG ER	824	411	$10,659.26	$0.41	$12.94	0.20%
BUPROPION TAB 100MG ER	290	155	$3,886.70	$0.42	$13.40	0.07%
BUPROPION TAB 200MG ER	114	44	$2,099.65	$0.62	$18.42	0.04%
WELLBUTRIN TAB XL 150MG	20	4	$53,334.49	$74.08	$2,666.72	1.02%
WELLBUTRIN TAB XL 300MG	10	1	$15,344.60	$51.15	$1,534.46	0.29%
SUBTOTAL	**26,891**	**9,387**	**$610,482.36**	**$0.68**	**$22.70**	**11.70%**
DULOXETINE PRODUCTS						
DULOXETINE CAP 60MG	16,705	4,163	$444,977.85	$0.74	$26.64	8.53%
DULOXETINE CAP 30MG	7,915	3,126	$179,948.79	$0.69	$22.74	3.45%
DULOXETINE CAP 20MG	1,218	526	$35,006.91	$0.92	$28.74	0.67%
CYMBALTA CAP 60MG	11	2	$6,913.03	$15.36	$628.46	0.13%
CYMBALTA CAP 30MG	1	1	$686.54	$7.63	$686.54	0.01%
SUBTOTAL	**25,850**	**7,818**	**$667,533.12**	**$0.74**	**$25.82**	**12.79%**
MIRTAZAPINE PRODUCTS						
MIRTAZAPINE TAB 15MG	11,485	3,526	$95,514.38	$0.26	$8.32	1.83%
MIRTAZAPINE TAB 30MG	6,980	2,037	$65,097.06	$0.29	$9.33	1.25%
MIRTAZAPINE TAB 45MG	3,189	732	$42,250.12	$0.38	$13.25	0.81%
MIRTAZAPINE TAB 7.5MG	728	265	$37,815.30	$1.72	$51.94	0.73%
MIRTAZAPINE 15MG ODT	241	82	$6,842.72	$0.91	$28.39	0.13%
MIRTAZAPINE 30MG ODT	121	43	$3,965.15	$0.94	$32.77	0.08%
MIRTAZAPINE 45MG ODT	26	8	$792.57	$0.97	$30.48	0.02%
SUBTOTAL	**22,770**	**6,693**	**$252,277.30**	**$0.35**	**$11.08**	**4.85%**
VENLAFAXINE PRODUCTS						
VENLAFAXINE CAP 150MG ER	7,995	2,053	$86,024.35	$0.30	$10.76	1.65%
VENLAFAXINE CAP 75MG ER	6,330	2,350	$55,935.48	$0.25	$8.84	1.07%
VENLAFAXINE TAB 75MG	2,315	693	$37,947.29	$0.52	$16.39	0.73%
VENLAFAXINE CAP 37.5 ER	2,296	1,220	$18,396.54	$0.24	$8.01	0.35%
VENLAFAXINE TAB 37.5MG	917	394	$13,393.37	$0.48	$14.61	0.26%
VENLAFAXINE TAB 100MG	482	117	$9,796.95	$0.66	$20.33	0.19%
VENLAFAXINE TAB 50MG	186	64	$3,143.67	$0.55	$16.90	0.06%
VENLAFAXINE TAB 25MG	152	65	$2,314.69	$0.49	$15.23	0.04%
EFFEXOR XR CAP 150MG	38	4	$25,153.02	$22.06	$661.92	0.48%
EFFEXOR XR CAP 75MG	18	2	$13,158.71	$19.94	$731.04	0.25%
SUBTOTAL	**20,729**	**6,962**	**$265,264.07**	**$0.37**	**$12.80**	**5.08%**
PAROXETINE PRODUCTS						
PAROXETINE TAB 20MG	5,522	2,207	$33,783.34	$0.17	$6.12	0.65%
PAROXETINE TAB 40MG	3,887	1,035	$33,247.23	$0.23	$8.55	0.64%
PAROXETINE TAB 10MG	2,301	957	$14,828.65	$0.19	$6.44	0.28%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
PAROXETINE TAB 30MG	1,721	469	$14,273.30	$0.24	$8.29	0.27%
PAXIL SUS 10MG/5ML	56	12	$11,300.03	$6.88	$201.79	0.22%
PAXIL TAB 40MG	4	1	$2,324.60	$6.46	$581.15	0.04%
SUBTOTAL	**13,491**	**4,681**	**$109,757.15**	**$0.23**	**$8.14**	**2.10%**
FLUVOXAMINE PRODUCTS						
FLUVOXAMINE TAB 100MG	1,290	273	$23,697.33	$0.60	$18.37	0.45%
FLUVOXAMINE TAB 50MG	1,005	246	$13,142.86	$0.43	$13.08	0.25%
FLUVOXAMINE TAB 25MG	359	95	$4,136.10	$0.37	$11.52	0.08%
SUBTOTAL	**2,654**	**614**	**$40,976.29**	**$0.50**	**$15.44**	**0.78%**
TIER-1 SUBTOTAL	**377,470**	**69,648***	**$3,906,883.91**	**$0.31**	**$10.35**	**74.91%**
TIER-2 MEDICATIONS						
VILAZODONE PRODUCTS						
VIIBRYD TAB 40MG	822	158	$178,577.62	$7.24	$217.25	3.42%
VIIBRYD TAB 20MG	241	91	$51,863.63	$7.29	$215.20	0.99%
VIIBRYD TAB 10MG	52	35	$9,699.58	$7.37	$186.53	0.19%
VIIBRYD KIT	4	4	$804.20	$6.70	$201.05	0.02%
SUBTOTAL	**1,119**	**288**	**$240,945.03**	**$7.26**	**$215.32**	**4.62%**
TIER-2 SUBTOTAL	**1,119**	**242***	**$240,945.03**	**$7.26**	**$215.32**	**4.62%**
TIER-3 MEDICATIONS						
DESVENLAFAXINE PRODUCTS						
PRISTIQ TAB 100MG	259	53	$103,152.55	$10.34	$398.27	1.98%
PRISTIQ TAB 50MG	257	64	$107,334.52	$9.96	$417.64	2.06%
PRISTIQ TAB 25MG	23	6	$6,615.89	$10.21	$287.65	0.13%
DESVENLAFAX 100MG ER	13	4	$1,923.73	$4.93	$147.98	0.04%
DESVENLAFAX 50MG ER	10	5	$1,495.10	$4.98	$149.51	0.03%
SUBTOTAL	**562**	**132**	**$220,521.79**	**$9.98**	**$392.39**	**4.24%**
VORTIOXETINE PRODUCTS[+]						
BRINTELLIX TAB 20MG	134	41	$42,596.52	$10.67	$317.88	0.82%
TRINTELLIX TAB 20MG	133	43	$44,446.73	$11.20	$334.19	0.85%
BRINTELLIX TAB 10MG	82	35	$24,690.06	$10.20	$301.10	0.47%
TRINTELLIX TAB 10MG	64	33	$25,883.85	$12.22	$404.44	0.50%
BRINTELLIX TAB 5MG	11	4	$3,538.17	$10.72	$321.65	0.07%
TRINTELLIX TAB 5MG	6	4	$2,033.48	$11.30	$338.91	0.04%
SUBTOTAL	**430**	**160**	**$143,188.81**	**$11.00**	**$333.00**	**2.75%**
LEVOMILNACIPRAN PRODUCTS[Δ]						
FETZIMA CAP 80MG	144	39	$44,839.42	$10.38	$311.38	0.86%
FETZIMA CAP 40MG	120	48	$37,714.10	$10.59	$314.28	0.72%
FETZIMA CAP 120MG	67	17	$21,247.21	$10.57	$317.12	0.41%
FETZIMA CAP 20MG	17	12	$4,596.93	$10.13	$270.41	0.09%
FETZIMA CAP TITRATION	6	5	$1,774.82	$10.56	$295.80	0.03%
SUBTOTAL	**354**	**121**	**$110,172.48**	**$10.48**	**$311.22**	**2.11%**
NEFAZODONE PRODUCTS						
NEFAZODONE TAB 200MG	23	3	$1,294.81	$1.88	$56.30	0.02%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
NEFAZODONE TAB 100MG	16	3	$1,038.91	$2.16	$64.93	0.02%
NEFAZODONE TAB 250MG	11	1	$712.35	$1.93	$64.76	0.01%
NEFAZODONE TAB 150MG	8	2	$599.26	$2.00	$74.91	0.01%
SUBTOTAL	**58**	**9**	**$3,645.33**	**$1.98**	**$62.85**	**0.06%**
SELEGILINE PRODUCTS						
EMSAM DIS 12MG/24H	5	1	$7,988.65	$53.26	$1,597.73	0.15%
EMSAM DIS 6MG/24HR	2	1	$3,203.46	$53.39	$1,601.73	0.06%
SUBTOTAL	**7**	**2**	**$11,192.11**	**$53.30**	**$1,598.87**	**0.21%**
TRANYLCYPROMINE PRODUCTS						
TRANYLCYPROM TAB 10MG	5	1	$1,538.54	$11.74	$307.71	0.03%
SUBTOTAL	**5**	**1**	**$1,538.54**	**$11.74**	**$307.71**	**0.03%**
TIER-3 SUBTOTAL	**1,416**	**302***	**$490,259.06**	**$10.26**	**$346.23**	**9.40%**
SPECIAL PA MEDICATIONS						
VENLAFAXINE PRODUCTS						
VENLAFAXINE TAB 225MG ER	1,027	239	$293,869.10	$7.76	$286.14	5.64%
VENLAFAXINE TAB 150MG ER	175	56	$20,626.17	$2.94	$117.86	0.40%
VENLAFAXINE TAB 75MG ER	63	32	$6,194.68	$2.89	$98.33	0.12%
VENLAFAXINE TAB 37.5MG ER	47	16	$4,223.67	$3.24	$89.87	0.08%
SUBTOTAL	**1,312**	**343**	**$324,913.62**	**$6.72**	**$247.65**	**6.24%**
PAROXETINE PRODUCTS						
PAROXETINE TAB 25MG ER	510	126	$72,140.30	$4.26	$141.45	1.38%
PAROXETIN TAB 37.5MG ER	183	56	$30,625.51	$4.15	$167.35	0.59%
PAROXETIN TAB 12.5MG ER	132	58	$16,307.49	$3.82	$123.54	0.31%
PEXEVA TAB 20MG	8	2	$7,372.16	$11.17	$921.52	0.14%
PAXIL CR TAB 37.5MG	8	1	$1,505.34	$6.27	$188.17	0.03%
PEXEVA TAB 40MG	1	1	$1,095.05	$12.17	$1,095.05	0.02%
SUBTOTAL	**842**	**244**	**$129,045.85**	**$4.37**	**$153.26**	**2.47%**
FLUVOXAMINE PRODUCTS						
FLUVOXAMINE CAP 100MG	175	28	$73,137.69	$13.62	$417.93	1.40%
FLUVOXAMINE CAP 150MG	123	23	$38,461.42	$9.64	$312.69	0.74%
SUBTOTAL	**298**	**51**	**$111,599.11**	**$11.92**	**$374.49**	**2.14%**
FLUOXETINE PRODUCTS						
FLUOXETINE CAP 90MG DR	46	8	$6,220.34	$4.81	$135.22	0.12%
FLUOXETINE TAB 60MG	15	3	$3,644.16	$8.10	$242.94	0.07%
SUBTOTAL	**61**	**11**	**$9,864.50**	**$5.66**	**$161.71**	**0.19%**
BUPROPION PRODUCTS						
FORFIVO XL TAB 450MG	1	1	$350.50	$11.68	$350.50	0.02%
SUBTOTAL	**1**	**1**	**$350.50**	**$11.68**	**$350.50**	**0.02%**
DULOXETINE PRODUCTS						
DULOXETINE CAP 40MG	1	1	$104.14	$3.47	$104.14	0.01%
SUBTOTAL	**1**	**1**	**$104.14**	**$3.47**	**$104.14**	**0.01%**
SPECIAL PA SUBTOTAL	**2,515**	**589***	**$575,877.72**	**$6.47**	**$228.98**	**11.07%**
TOTAL	**382,520**	**69,990***	**$5,213,965.72**	**$0.41**	**$13.63**	**100.00%**

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

[+]The FDA approved a brand name change for Brintellix® (vortioxetine) to Trintellix® in May 2016; therefore, the product was still available as Brintellix® for part of calendar year 2016, as is reflected in the utilization details above.

[Δ]The levomilnacipran products moved from Tier-2 to Tier-3 on January 1, 2017. The utilization above occurred during calendar year 2016, but is shown under the Tier-3 products to reflect the current tier placement.

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Appendix Q

Calendar Year 2016 Annual Review of Fibric Acid Derivative Medications and 30-Day Notice to Prior Authorize Choline Fenofibrate Delayed-Release (Trilipix®) 135mg Capsules and Fenofibrate Micronized (Lofibra®) 200mg Capsules

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Fibric Acid Derivative Medications	
Tier-1	**Tier-2**
choline fenofibrate delayed-release (Trilipix® capsules)	fenofibrate (Fenoglide® tablets)
fenofibrate (Tricor® tablets)	fenofibrate (Lipofen® capsules)
fenofibrate (Triglide® tablets) 160mg	fenofibrate micronized (Antara® capsules)
fenofibrate micronized (Lofibra® capsules)	fenofibric acid (Fibricor® tablets)
gemfibrozil (Lopid® tablets)	

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

Fibric Acid Derivative Tier-2 Approval Criteria:

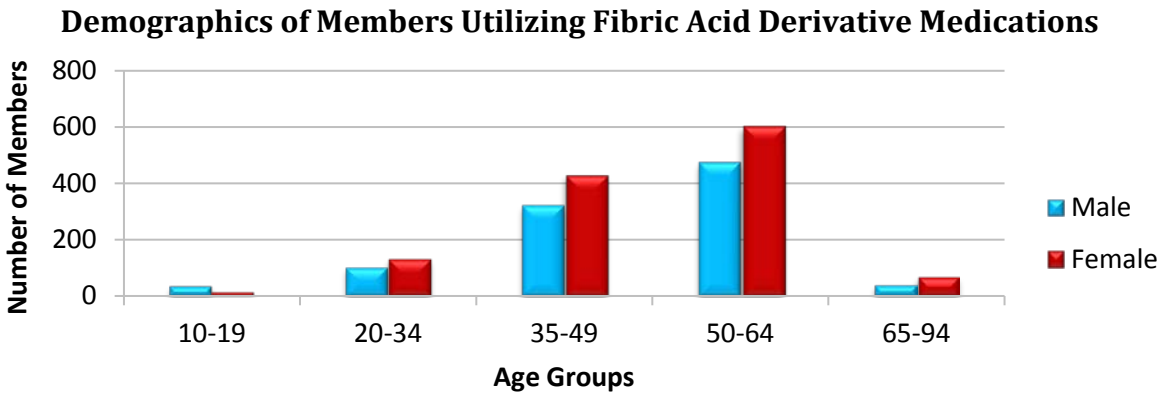
1. Laboratory documented failure with a Tier-1 medication after a six month trial; or
2. Documented adverse effect, drug interaction, or contraindication to all Tier-1 medication(s); or
3. Prior stabilization on the Tier-2 medication documented within the last 100 days.

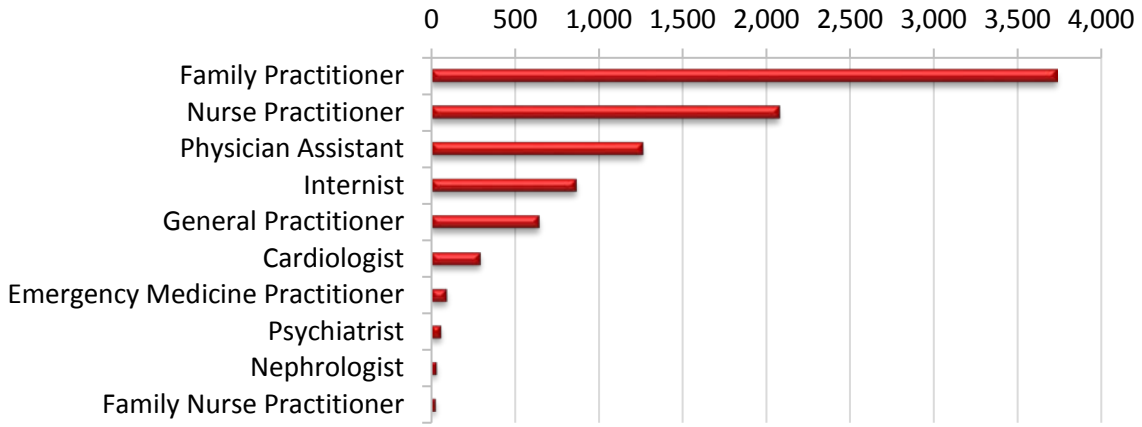
Utilization of Fibric Acid Derivative Medications: Calendar Year 2016

Comparison of Calendar Years

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	2,219	9,544	$458,971.64	$48.09	$1.21	475,013	377,933
2016	2,215	9,283	$363,777.73	$39.19	$0.96	475,386	378,270
% Change	**-0.20%**	**-2.70%**	**-20.70%**	**-18.50%**	**-20.70%**	**0.10%**	**0.10%**
Change	**-4**	**-261**	**-$95,193.91**	**-$8.90**	**-$0.25**	**373**	**337**

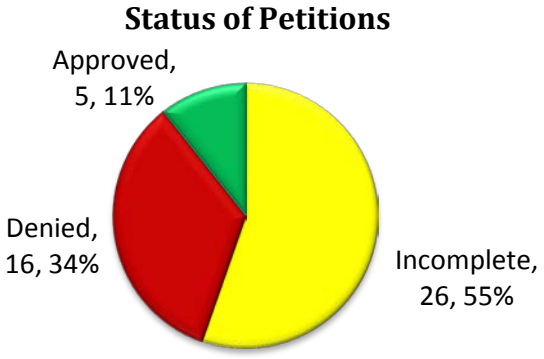
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.





Prior Authorization of Fibric Acid Derivative Medications

There were 47 prior authorization requests for 33 unique members submitted for fibric acid derivative medications during calendar year 2016. The following chart shows the status of the submitted petitions.



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

Anticipated Patent Expiration(s):

- Tricor® (fenofibrate): January 2018
- Triglide® (fenofibrate): September 2021
- Fenoglide® (fenofibrate): October 2024

- Trilipix® (choline fenofibrate delayed-release): January 2025
- Antara® (micronized fenofibrate): April 2025
- Fibricor® (fenofibric acid): August 2027

News:

- **April 2016:** The U.S. Food and Drug Administration (FDA) withdrew approval of the indications related to the coadministration with a statin for niacin extended-release (ER) tablets and fenofibric acid delayed-release (DR) capsules. This decision was based on results of several large cardiovascular outcomes trials which concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-cholesterol levels in statin-treated patients results in reduction in the risk of cardiovascular events. Based on this conclusion, the FDA determined that the benefits from niacin ER tablets and fenofibric acid DR capsules for coadministration with statins no longer outweighed the risks.
- **April 2017:** The American Association of Clinical Endocrinologists (AACE) released updated guidelines for the management of dyslipidemia and prevention of cardiovascular disease. Key updates compared to the previous guidelines include the following:
    - The 2017 atherosclerotic cardiovascular disease (ASCVD) risk factor modifications algorithm for patients with type 2 diabetes mellitus (T2DM) now includes an "extreme" risk category, defined as a diagnosis of T2DM plus a prior ASCVD event (i.e. established clinical cardiovascular disease).
    - The new algorithm for T2DM focuses on lipid management goals for LDL-C, non-HDL-C, triglycerides (TG), and apolipoprotein (ApoB), while removing target levels for total cholesterol (TC), HDL-C, and LDL-P.
    - Treatment goals in the new "extreme" category include LDL-C < 55mg/dL, non-HDL-C < 80mg/dL, TG < 150mg/dL, and ApoB < 70mg/dL.
    - Additional major independent risk factors for ASCVD listed in the updated guidelines include polycystic ovary syndrome (PCOS), chronic kidney disease (CKD) stage 3 and 4, and evidence of coronary artery calcification.

Pipeline Update(s):

- **Pemafibrate:** Kowa Research Institute Inc. is conducting a multi-centered, randomized, placebo controlled Phase 3 trial for pemafibrate for the treatment of dyslipidemia in patients with T2DM, which is aiming to recruit an estimated 10,000 high-risk diabetic patients worldwide. The primary objective of the study is to determine if pemafibrate 0.2mg twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of 1) nonfatal myocardial infarction, 2) nonfatal ischemic stroke, 3) hospitalization for unstable angina requiring unplanned coronary revascularization, or 4) cardiovascular death. Pemafibrate is a potent selective peroxisome proliferator-activated receptor (PPAR)-α modulator that is at least 1,000 times as potent and selective as other drugs in this class.

Cost Comparison[7]

Fibric acid derivatives come in a variety of formulations (i.e. fenofibrate, fenofibrate micronized, fenofibric acid, and choline fenofibrate delayed-release) and strengths for the treatment of dyslipidemia, including hyperlipidemia and hypertriglyceridemia. The primary difference between the various products is that the different formulations vary in relation to food effect and are not equivalent on a milligram-to-milligram basis because of their bioavailability. The cost of choline fenofibrate delayed-release (Trilipix®) 135mg capsules and fenofibrate micronized (Lofibra®) 200mg capsules differs greatly from the cost of other comparable fibric acid derivative products. The National Average Drug Acquisition Cost (NADAC) of choline fenofibrate delayed-release (Trilipix®) 135mg capsules and fenofibrate micronized (Lofibra®) 200mg capsules is $1.61 and $1.75 per capsule, respectively. This results in a 30-day supply costing $48.30 and $52.50. As shown below, a 30-day supply of the other available comparable fibric acid derivative products is between $15.60 and $33.60, which is less by almost $15.00 or more per month.

Cost Comparison:

Medication	Cost Per Unit	Cost for 30 Days of Therapy*
choline fenofibrate delayed-release (Trilipix® capsules) 135mg	**$1.61**	**$48.30**
fenofibrate micronized (Lofibra® capsules) 200mg	**$1.75**	**$52.50**
fenofibrate (Lofibra® capsules) 160mg	$0.52	$15.60
fenofibrate (Tricor® tablets) 145mg	$0.91	$27.30
fenofibrate (Triglide® tablets) 160mg	$1.12	$33.60

*30 days of therapy based on usual dose of medication
Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC) or State Maximum Allowable Cost (SMAC) if NADAC unavailable.

Recommendations

The College of Pharmacy recommends the following changes to the fibric acid derivative medication Product Based Prior Authorization (PBPA) category:

1. Move fenofibric acid (Fibricor®) 35mg tablets into Tier-1 based on low net cost.
2. Move choline fenofibrate delayed-release (Trilipix®) 135mg capsules and fenofibrate micronized (Lofibra®) 200mg capsules into Tier-2 based on net cost. Current Tier-2 criteria will apply.

Fibric Acid Derivative Medications	
Tier-1	**Tier-2**
choline fenofibrate delayed-release (Trilipix® capsules) 48mg	**choline fenofibrate delayed-release (Trilipix® capsules) 135mg**
fenofibrate (Tricor® tablets)	fenofibrate (Fenoglide® tablets)
fenofibrate (Triglide® tablets) 160mg	fenofibrate (Lipofen® capsules)
fenofibrate micronized (Lofibra® capsules)	fenofibrate micronized (Antara® capsules)
fenofibric acid (Fibricor® tablets) 35mg	**fenofibrate micronized (Lofibra® capsules) 200mg**
gemfibrozil (Lopid® tablets)	fenofibric acid (Fibricor® tablets) 105mg

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

Utilization Details of Fibric Acid Derivative Medications: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TIER-1 PRODUCTS					
GEMFIBROZIL TAB 600MG	3,153	760	$28,841.33	4.15	$9.15
FENOFIBRATE TAB 145MG	2,275	579	$109,213.82	3.93	$48.01
FENOFIBRATE TAB 160MG	1,402	313	$50,357.02	4.48	$35.92
FENOFIBRIC CAP 135MG DR	774	201	$92,611.22	3.85	$119.65
FENOFIBRATE TAB 48MG	552	167	$17,265.28	3.31	$31.28
FENOFIBRATE MICRONIZED CAP 134MG	322	84	$20,669.39	3.83	$64.19
FENOFIBRATE TAB 54MG	282	89	$7,066.85	3.17	$25.06
FENOFIBRIC CAP 45MG DR	245	63	$11,074.52	3.89	$45.20
FENOFIBRATE MICRONIZED CAP 200MG	165	28	$12,186.61	5.89	$73.86
FENOFIBRATE MICRONIZED CAP 67MG	64	11	$1,874.18	5.82	$29.28
SUBTOTAL	**9,234**	**2,295**	**$351,160.22**	**4.23**	**$38.03**
TIER-2 PRODUCTS					
FENOFIBRATE CAP 150MG	17	4	$2,884.77	4.25	$169.69
FENOFIBRATE TAB 40 MG	11	1	$3,813.72	11	$346.70
FENOFIBRATE TAB 40MG	11	3	$3,441.99	3.67	$312.91
FENOFIBRATE MICRONIZED CAP 130MG	4	1	$645.95	4	$161.49
FENOFIBRATE CAP 50 MG	2	1	$574.72	2	$287.36
FENOFIBRIC ACID TAB 105MG	2	2	$303.67	1	$151.84
FENOFIBRATE MICRONIZED CAP 43MG	1	1	$158.70	1	$158.70
FENOFIBRATE TAB 120MG	1	1	$793.99	1	$793.99
SUBTOTAL	**49**	**14**	**$12,617.51**	**3.49**	**$257.50**
TOTAL	**9,283**	**2,215***	**$363,777.73**	**4.19**	**$39.19**

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

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Appendix R

Calendar Year 2016 Annual Review of Fibromyalgia Medications

Oklahoma Health Care Authority
July 2017

Current Prior Authorization Criteria

Fibromyalgia Medications		
Tier-1	**Tier-2***	**Tier-3**
amitriptyline (Elavil®)	milnacipran (Savella®)	pregabalin (Lyrica®)
cyclobenzaprine (Flexeril®)		
duloxetine (Cymbalta®)		
fluoxetine (Prozac®)		
tramadol (Ultram®)		

*Tier-2 will include supplemental rebated medications. If no medications rebate to Tier-2, Tier-2 will include the lowest net cost Tier-3 product(s).
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Fibromyalgia Medications Tier-2 Approval Criteria:

1. A documented, recent (within the last six months) trial of two Tier-1 medications (must include one trial with duloxetine) at least three weeks in duration that did not provide an adequate response or resulted in intolerable adverse effects; or
2. Contraindication(s) to all available lower tiered medications; or
3. Current stabilization on a Tier-2 medication.
4. Clinical Exceptions include:
    a. Diagnosis of seizures or postherpetic neuralgia for Lyrica® (pregabalin).

Fibromyalgia Medications Tier-3 Approval Criteria:

1. A documented, recent (within the last six months) trial of two Tier-1 medications (must include one trial with duloxetine) and all available Tier-2 medications at least three weeks in duration that did not provide an adequate response or resulted in intolerable adverse effects; or
2. Contraindication(s) to all available lower tiered medications; or
3. Current stabilization on a Tier-3 medication.

Lyrica® (Pregabalin) Approval Criteria [Diabetic Neuropathy Diagnosis]:

1. For the diagnosis of diabetic neuropathy, a trial of duloxetine and a trial of gabapentin or a patient-specific, clinically significant reason why duloxetine or gabapentin cannot be used must be provided.
2. Clinical exceptions for Lyrica® (pregabalin) include:
    a. Diagnosis of seizures or postherpetic neuralgia.

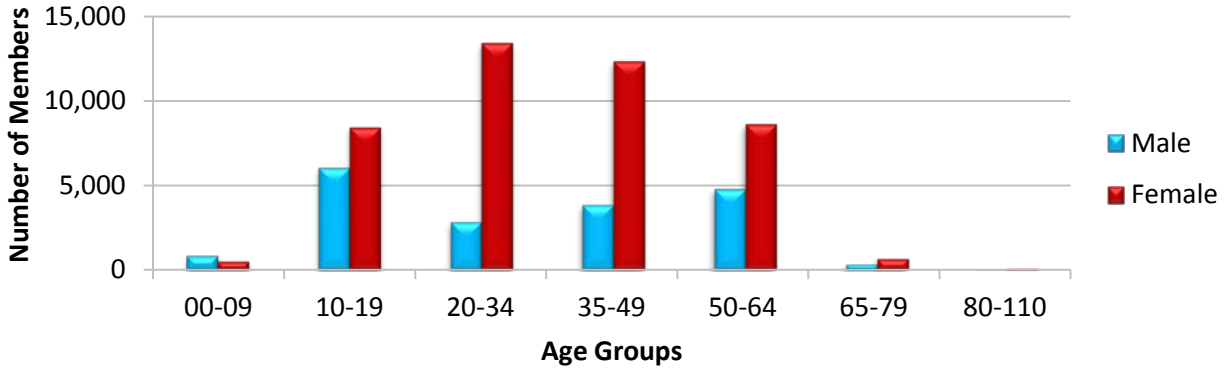
Utilization of Fibromyalgia Medications: Calendar Year 2016

Comparison of Calendar Years

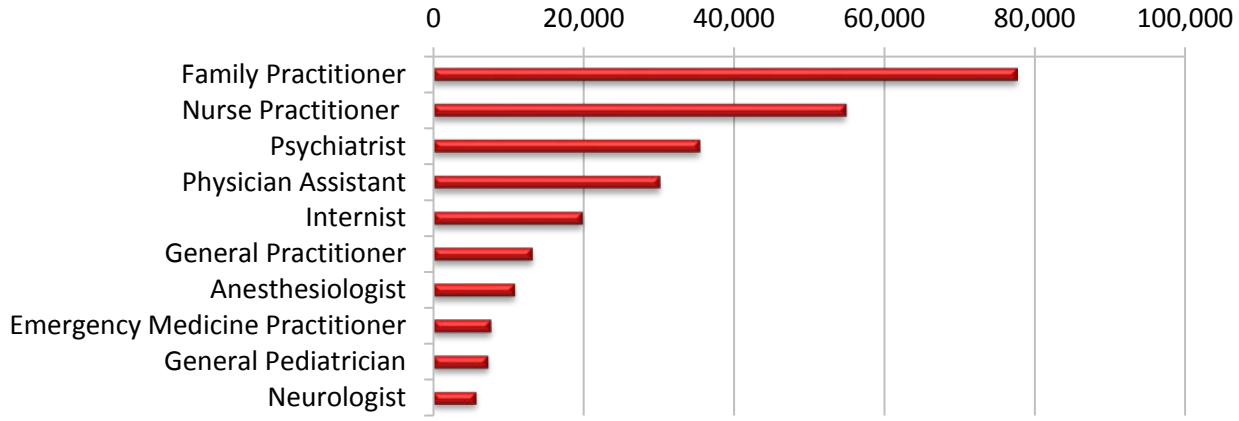
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	63,100	278,574	$8,019,253.02	$28.79	$1.02	18,309,443	7,894,616
2016	62,875	287,822	$7,773,231.99	$27.01	$0.93	19,344,059	8,333,446
% Change	**-0.40%**	**3.30%**	**-3.10%**	**-6.20%**	**-8.80%**	**5.70%**	**5.60%**
Change	**-225**	**9,248**	**-$246,021.03**	**-$1.78**	**-$0.09**	**1,034,616**	**438,830**

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

Demographics of Members Utilizing Fibromyalgia Medications

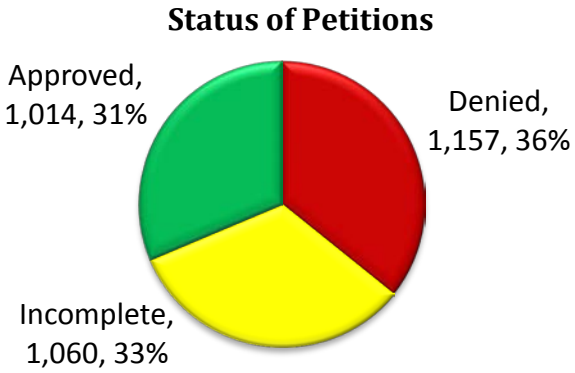


Top Prescriber Specialties of Fibromyalgia Medications by Number of Claims



Prior Authorization of Fibromyalgia Medications

There were 3,231 prior authorization requests submitted for fibromyalgia medications during calendar year 2016. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions for calendar year 2016.



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

Anticipated Patent Expiration(s):

- Lyrica® (pregabalin): December 2018
- Savella® (milnacipran): November 2021

News:

- **July 2016:** The European League Against Rheumatism (EULAR) released updated guidelines for fibromyalgia management. Compared to the previous recommendations from 2008, the only updated medication recommendation was the SSRI's (fluoxetine). This recommendation went from a recommendation of *weak for* to a recommendation of *weak against* based on updated literature. The SoonerCare fibromyalgia tier chart has been updated to reflect this change (*see recommendations section)*.
- **January 2017:** The American Diabetes Association (ADA) released a position statement on diabetic neuropathy prevention, diagnosis, and management. Pain management recommendations from the position statement include duloxetine, gabapentin, pregabalin, and tricyclic antidepressants (TCAs) even though they are not FDA approved for this indication.
- **June 2017:** A new study showed that radiographic evidence of axial spondyloarthritis is common in patients with a diagnosis of fibromyalgia syndrome. The study included 99 patients who met the American College of Rheumatology 1990 criteria for fibromyalgia syndrome. Patients were examined by magnetic resonance imaging (MRI) for features of spondyloarthritis based on the Assessment of Spondyloarthritis International Society (ASIS) criteria. The results of the study showed a positive correlation between C-reactive protein levels and axial spondyloarthritis, with an odds ratio of 5.1; a total of 31.5% of subjects had an elevated level. The results also showed that 8.1% had sacroiliitis and 10.2% met ASIS criteria for axial spondyloarthritis. A significant number of subjects also had radiographic changes that indicated inflammatory involvement (17% demonstrated erosion, 25% had subchondral sclerosis).

Pipeline Update(s):

- **IMC-1:** A 16-week, randomized, double-blinded, placebo-controlled Phase 2 study of IMC-1 (a combination of famciclovir and celecoxib) demonstrated a significant decrease in fibromyalgia-related pain compared to placebo. Over 50% of the IMC-1-treated patients had at least a 30% reduction of pain and 38% achieved at least 50% reduction

in pain during the study. Additionally, IMC-1 showed a statistically significant reduction in self-reported fatigue with the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue inventory developed by the National Institute of Health (NIH). The U.S. Food and Drug Administration (FDA) has granted IMC-1 fast track status and a Phase 3 study is planned to begin this year.

- **Mirogabalin:** Daiichi-Sankyo is developing a novel, preferentially selective α2δ-1 ligand characterized by high potency and selectivity to the α2δ-1 subunit of voltage-sensitive calcium-channel complexes in the central nervous system. Mirogabalin has also demonstrated to have a unique binding profile and long duration of action. Mirogabalin is currently undergoing Phase 3 clinical trials for treatment of pain associated with fibromyalgia and peripheral neuropathic pain (i.e. diabetic peripheral neuropathy and postherpetic neuralgia). One report states mirogabalin is reporting a high rate of adverse effects, including suicidal ideation and liver function abnormalities, however, Daiichi-Sanyko has not publically announced any safety or efficacy concerns. Results are expected to be released during calendar year 2017.
- **TNX-102 SL:** In September 2016, Tonix Pharmaceuticals announced it will halt development of TNX-102 SL (proposed tradename Tonmya™), a sublingual cyclobenzaprine 2.8mg tablet, as a drug candidate for the treatment of fibromyalgia after it failed to achieve a target primary endpoint of a statistically significant proportion of patients reporting 30% or greater reduction in pain from baseline to the end of the 12-week treatment period in the AFFIRM Phase 3 trial. When TNX-102 SL activity in fibromyalgia was cross-validated by two additional endpoints, Patient Global Impression of Change (PGIC) and the Revised Fibromyalgia Impact Questionnaire (FIQ-R) assessing global fibromyalgia symptom and function improvement, the drug showed strong improved sleep quality effects by both the daily diary and sleep disturbance scale. Based on the results of these additional endpoints, Tonix announced that they plan to study TNX-102 SL for the treatment of post-traumatic stress disorder (PTSD).

Recommendations

The College of Pharmacy has removed fluoxetine as a Tier-1 fibromyalgia trial option based on updated treatment guidelines. Changes can be seen in red in the following Fibromyalgia Tier chart. The College of Pharmacy does not recommend any further changes at this time.

Fibromyalgia Medications		
Tier-1	**Tier-2***	**Tier-3**
amitriptyline (Elavil®)	milnacipran (Savella®)	pregabalin (Lyrica®)
cyclobenzaprine (Flexeril®)		
duloxetine (Cymbalta®)		
~~**fluoxetine (Prozac®)**~~		
tramadol (Ultram®)		

*Tier-2 will include supplemental rebated medications. If no medications rebate to Tier-2, Tier-2 will include the lowest net cost Tier-3 product(s).

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

Utilization Details of Fibromyalgia Medications: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TIER-1 UTILIZATION					
AMITRIPTYLINE PRODUCTS					
AMITRIPTYLIN TAB 25MG	6,036	2,367	$64,435.83	2.55	$10.68
AMITRIPTYLIN TAB 50MG	4,425	1,434	$84,033.72	3.09	$18.99
AMITRIPTYLIN TAB 10MG	3,422	1,346	$28,213.87	2.54	$8.24
AMITRIPTYLIN TAB 100MG	2,620	647	$103,859.14	4.05	$39.64
AMITRIPTYLIN TAB 150MG	1,109	231	$70,369.63	4.8	$63.45
AMITRIPTYLIN TAB 75MG	918	267	$26,168.45	3.44	$28.51
SUBTOTAL	**18,530**	**5,461***	**$377.080.64**	**3.39**	**$20.35**
CYCLOBENZAPRINE PRODUCTS					
CYCLOBENZAPR TAB 10MG	33,846	16,035	$153,573.93	2.11	$4.54
CYCLOBENZAPR TAB 5MG	6,904	4,447	$37,618.00	1.55	$5.45
AMRIX CAP 15MG	1	1	$102.85	1	$102.85
SUBTOTAL	**40,751**	**19,817***	**$191,294.78**	**2.06**	**$4.69**
DULOXETINE PRODUCTS					
DULOXETINE CAP 60MG	16,705	4,163	$444,977.85	4.01	$26.64
DULOXETINE CAP 30MG	7,915	3,126	$179,948.79	2.53	$22.74
DULOXETINE CAP 20MG	1,221	527	$35,006.91	2.32	$28.72
CYMBALTA CAP 60MG	11	2	$6,913.03	5.5	$628.46
CYMBALTA CAP 30MG	1	1	$686.54	1	$686.54
DULOXETINE CAP 40MG	1	1	$104.14	1	$104.14
SUBTOTAL	**25,854**	**6,391***	**$667,637.26**	**4.05**	**$25.83**
FLUOXETINE PRODUCTS					
FLUOXETINE CAP 20MG	27,508	8,703	$132,683.65	3.16	$4.82
FLUOXETINE CAP 40MG	14,024	3,759	$123,668.81	3.73	$8.82
FLUOXETINE CAP 10MG	11,559	4,196	$60,033.95	2.75	$5.19
FLUOXETINE TAB 10MG	3,602	1,236	$98,983.81	2.91	$27.48
FLUOXETINE TAB 20MG	2,305	844	$127,160.45	2.73	$55.17
FLUOXETINE SOL 20MG/5ML	1,231	290	$12,171.26	4.24	$9.89
FLUOXETINE CAP 90MG DR	46	8	$6,220.34	5.75	$135.22
PROZAC CAP 20MG	21	3	$20,135.89	7	$958.85
FLUOXETINE TAB 60MG	15	3	$3,644.16	5	$242.94
PROZAC CAP 40MG	9	1	$13,265.24	9	$1,473.92
SUBTOTAL	**60,320**	**14,666***	**$597,967.56**	**4.11**	**$9.91**
GABAPENTIN PRODUCTS					
GABAPENTIN CAP 300MG	35,527	11,017	$273,405.25	3.22	$7.70
GABAPENTIN TAB 600MG	21,870	4,751	$461,718.40	4.6	$21.11
GABAPENTIN TAB 800MG	13,294	2,455	$298,429.59	5.42	$22.45
GABAPENTIN CAP 100MG	8,828	3,445	$51,666.42	2.56	$5.85
GABAPENTIN CAP 400MG	5,337	1,475	$49,970.56	3.62	$9.36
GABAPENTIN SOL 250/5ML	675	134	$38,706.96	5.04	$57.34
NEURONTIN CAP 300MG	12	1	$4,312.41	12	$359.37

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
NEURONTIN TAB 800MG	12	1	$9,502.87	12	$791.91
GABAPENTIN SOL 300/6ML	1	1	$35.28	1	$35.28
SUBTOTAL	**85,556**	**18,689***	**$1,187,747.74**	**4.58**	**$13.88**
TRAMADOL PRODUCTS					
TRAMADOL HCL TAB 50MG	46,054	18,368	$249,650.66	2.51	$5.42
TRAMADOL HCL TAB 200MG ER	4	1	$382.34	4	$95.59
TRAMADOL HCL TAB 100MG ER	1	1	$61.38	1	$61.38
SUBTOTAL	**46,059**	**18,369***	**$250,094.38**	**2.51**	**$5.43**
TIER-1 SUBTOTAL	**277,070**	**62,375***	**$3,271,886.97**	**4.44**	**$11.81**
TIER-2 UTILIZATION					
MILNACIPRAN PRODUCTS					
SAVELLA TAB 100MG	129	19	$37,650.92	6.79	$291.87
SAVELLA TAB 50MG	113	33	$32,078.20	3.42	$283.88
SAVELLA MIS TITR PAK	30	29	$8,068.34	1.03	$268.94
SAVELLA TAB 25MG	23	13	$5,938.69	1.77	$258.20
SAVELLA TAB 12.5MG	19	13	$4,166.18	1.46	$219.27
SUBTOTAL	**314**	**82***	**$87,902.33**	**3.83**	**$279.94**
TIER-2 SUBTOTAL	**314**	**82***	**$87,902.33**	**3.83**	**$279.94**
TIER-3 UTILIZATION					
PREGABALIN PRODUCTS					
LYRICA CAP 150MG	3,250	552	$1,379,963.89	5.89	$424.60
LYRICA CAP 75MG	1,987	464	$833,228.86	4.28	$419.34
LYRICA CAP 100MG	1,920	373	$871,391.92	5.15	$453.85
LYRICA CAP 300MG	1,085	161	$419,826.23	6.74	$386.94
LYRICA CAP 200MG	905	139	$351,438.32	6.51	$388.33
LYRICA CAP 50MG	855	233	$363,315.16	3.67	$424.93
LYRICA CAP 225MG	359	56	$155,654.10	6.41	$433.58
LYRICA CAP 25MG	98	27	$37,954.48	3.63	$387.29
LYRICA SOL 20MG/ML	3	1	$880.90	3	$293.63
SUBTOTAL	**10,462**	**1,542***	**$4,412,653.86**	**6.78**	**$421.87**
TIER-3 SUBTOTAL	**10,462**	**1,542***	**$4,412,653.86**	**6.78**	**$421.87**
TOTAL	**287,846**	**62,885***	**$7,773,443.16**	**4.58**	**$27.01**

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

[1] U.S. Food and Drug Administration (FDA): Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 05/2017. Last accessed 06/23/2017.
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Appendix S

Calendar Year 2016 Annual Review of Ocaliva® (Obeticholic Acid)

Oklahoma Health Care Authority
July 2017

Introduction[1]

Ocaliva® (obeticholic acid) is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Obeticholic acid is a farnesoid X receptor (FXR) agonist. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing new synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting secretion of bile by the liver, thus reducing hepatic exposure to bile acids. The recommended starting dose is 5mg once daily. Dosing should be titrated to the maximum recommended dose of 10mg daily, if adequate reduction in alkaline phosphatase and/or total bilirubin has not been achieved after three months.

Cost:

Medication	Cost Per Tablet	Cost Per 30 days
Ocaliva®(obeticholic acid) 5mg, 10mg tablets	**$190.00**	**$5,700.00**

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.

Current Prior Authorization Criteria

Ocaliva® (Obeticholic Acid) Approval Criteria:

1. An FDA approved diagnosis of primary biliary cholangitis (PBC); and
2. Member must have taken ursodeoxycholic acid (UDCA) at an appropriate dose for at least one year and prescriber must confirm patient compliance with UDCA and a lack of improvement in liver function tests; and
3. The prescriber must also confirm all of the following:
    a. PBC is not caused by a superimposed liver disease; and
    b. If the member has a superimposed liver disease, it is being adequately treated; and
    c. Proper timing of bile acid sequestrants if co-administered with UDCA (four hours before or four hours after); and
4. Ocaliva® must be taken in combination with UDCA. For Ocaliva® monotherapy consideration, the prescriber must document a patient-specific, clinically significant reason why the member is unable to take UDCA; and
5. A quantity limit of one tablet daily will apply.

Utilization of Ocaliva® (Obeticholic Acid): Calendar Year 2016

Ocaliva® (obeticholic acid) was approved by the U.S. Food and Drug Administration (FDA) in May 2016. There was no utilization of Ocaliva® during calendar year 2016.

Prior Authorization of Ocaliva® (Obeticholic Acid)

There were no prior authorization requests submitted for Ocaliva® (obeticholic acid) during calendar year 2016.

Market News and Updates[2,3]

Anticipated Patent Expiration(s):

- Ocaliva® (obeticholic acid): June 2033

Pipeline:

- **GSK2330672:** As many as 70% of people who have PBC are affected by pruritus. The current first-line treatment is UDCA, but its effectiveness is limited. The efficacy and safety of GSK2330672, a selective inhibitor of human ileal bile acid transporter (IBAT), was recently studied in a double-blind, randomized, placebo-controlled, crossover, Phase 2a study. Using three different complementary patient-reported outcome measurements, GSK2330672 showed greater effects than placebo in reducing itch intensity, as well as night-time sleep interference and daytime fatigue. GSK2330672 significantly decreased serum activity of autotaxin, which forms lysophosphatidic acid, a novel proposed pruritogen in cholestasis shedding further light on the potential mechanisms for cholestatic pruritus and the actions of the drug. In addition to improving symptoms of primary biliary cholangitis, this study showed that pharmacological inhibition of IBAT can be used as a therapeutic strategy to decrease the circulating bile acid pool in cholestatic patients. GSK2330672 decreased serum conjugated bile acids and resulted in a 50% decrease in total bile acid concentrations. Diarrhea, the most common adverse event associated with GSK2330672 treatment, might limit the long-term use of this drug.

Recommendations

The College of Pharmacy does not recommend any changes to the Ocaliva® (obeticholic acid) prior authorization criteria at this time.

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[1] Ocaliva® Prescribing Information. Intercept Pharmaceuticals, Inc. Available online at: https://ocaliva.com/ocaliva_pi.pdf. Last revised 05/2016. Last accessed 06/15/2017.

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Appendix T

Industry News and Updates

Oklahoma Health Care Authority
July 2017

Introduction

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

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

News:

- **Outcomes-Based Payment:** Outcomes-based payment, a method of setting the price of a drug based on how effective it is at treating a particular condition, has been discussed as a possible method to address the problem of high prices for prescription medications. A survey done by Avalere, a healthcare consulting firm, reported that of the 45 health plans surveyed, 70% of the plans were very enthusiastic about initiating outcomes-based payment contracts for pharmaceuticals and approximately 25% had already implemented them and reported that they were very successful.
- **Orphan Drug Act:** Since the 1983 Orphan Drug Act was passed, hundreds of treatments for diseases that affect a relatively small number of patients have been approved. Controversy surrounds the Act due to the high prices of the medications and allegations that some drug companies have twisted the law to their advantage. Payers say that manufacturers charge premium prices for the orphan drugs and payers are forced to pay for them as they are the only options available. Payers also state that it is difficult to rationalize spending such a high amount without knowing the long-term effectiveness of the orphan drugs. The manufacturers of orphan drugs argue that the cost to research and develop these medications is long, costly, and risky; some companies focus on a therapeutic area for several decades without any profit. Payers also feel that it is unsustainable to keep up with the rapid growth in orphan drug sales. According to market watcher EvaluatePharma, it is projected that worldwide annual sales from orphan drugs will grow twice as fast as the rate predicted for conventional drugs through 2020. Manufacturers of orphan drugs state that the concerns regarding the rapid growth in spending for orphan drugs is overblown. According to a published study in *Health Affairs*, the U.S. orphan drug expenditures will actually remain fairly stable in proportion to total pharmaceutical expenditure (8.8% in 2014 to 9.5% in 2018). Payers also say that manufacturers are gaming the Orphan Drug Act in order to receive government incentives as well as exclusivity rights. A loophole in the Orphan Drug Act allows manufacturers to receive market exclusivity for drugs that are already available in markets outside the United States. Another way manufacturers are taking unfair advantage of the Act is by artificially slicing the disease into smaller subgroups in order to gain orphan status (salami slicing). Priority review vouchers have also been sold for as

much as $350 million by manufacturers of orphan drugs. Manufacturers say that a small number of approved orphan drugs were not in the "spirit" of the law and PhRMA, the drug industry's trade association, condemns manufacturers who game the system. According to a study published in *Health Affairs*, at the time of the analysis, partial orphan drugs (older drugs repurposed for a rare disease) only accounted for 64 of the 316 (20%) brand-name orphan drugs approved by the U.S. Food and Drug Administration (FDA). Experts believe that approximately 3% of orphan drugs exploited loopholes in the Orphan Drug Act.

- **American Medical Association:** The American Medical Association (AMA) has firmly stated opposition to capping payments for Medicaid. The American Health Care Act, which was passed by the House in May, would drastically remake the program and would also rollback Medicaid expansion over two years. If the bill is passed by the Senate in its current form it would convert Medicaid from an open entitlement to a block grant or per-capita cap model. In this model, states would receive lump-sum payments from the government that would change according to a fixed formula instead of according to need. An AMA reference committee added a resolution to the Centers for Medicare and Medicaid (CMS) report making opposition to caps on federal Medicaid funding AMA policy.
- **Chondroitin Sulfate:** The latest published evidence on osteoarthritis treatment was presented at the Annual European Congress of Rheumatology. CONCEPT (ChONdroitin vs. CElecoxib vs. Placebo Trial), a clinical trial carried out by the pharmaceutical company IBSA, demonstrated that pharmaceutical grade chondroitin sulfate is as effective as celecoxib, an anti-inflammatory medication, and superior to placebo for pain reduction and improvement of functional disability in patients with knee osteoarthritis. MOSAIC (24 MOnth study on Structural changes in knee osteoarthritis Assessed by mrI with Chrondroitin sulfate), a multicenter, randomized, double blind, controlled and comparative study, showed that chondroitin sulfate delays the disease's progression and is as effective as celecoxib in the improvement of osteoarthritis symptoms. The study enrolled 194 patients with knee osteoarthritis with inflammation and moderate pain to assess the effects of chondroitin sulfate 1,200mg per day and celecoxib 200mg per day on the loss of cartilage volume in knee osteoarthritis. Patients receiving chondroitin sulfate experienced a statistically significant lower loss of cartilage volume after the first year of treatment versus those patients who received celecoxib.
- **Self-Monitoring Blood Glucose:** A randomized trial found glycemic control among non-insulin treated patients with type 2 diabetes mellitus (T2DM) was no better when patients performed self-monitoring of blood glucose (SMBG) compared to patients who did not self-monitor. The results of the randomized, controlled trial were published online in *JAMA Internal Medicine* and also presented at the 77th Scientific Sessions of the American Diabetes Association. Patients in the trial were enrolled in one of three groups: no SMBG, SMBG once per day, and SMBG once per day plus enhanced patient feedback, which included meter-reported automatic tailored messages. Neither of the SMBG groups showed superiority over non-SMBG in estimated adjusted mean hemoglobin A1c. The authors of the study noted that the findings should not be generalized to patients who are on insulin. The group stated that one-sized glucose

monitoring does not fit all and "patients and clinicians should engage in dialogue regarding SMBG with the current evidence suggesting that SMBG should not be routine for most patients with non-insulin treated T2DM." The authors also stated that patients and clinicians should consider the specific clinical situation to determine whether or not testing is appropriate.

New Drug Approval(s):

- **Epinephrine Prefilled Syringe:** In June 2017, the FDA approved Symjepi™, an epinephrine prefilled syringe, for the emergency treatment of allergic reactions (type I), including anaphylaxis. Each Symjepi™ prefilled syringe contains 0.3mg epinephrine. The company said it is also preparing to submit a second New Drug Application (NDA) for a junior version of the product.

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[3] Firth S. AMA Just Says No to Medicaid Cuts – Unified in opposition, the AMA remains divided on how to handle the details. *Medpage Today*. Available online at: https://www.medpagetoday.com/meetingcoverage/ama/65975?xid=nl_mpt_DHE_2017-06-15&eun=g720351d0r&pos=7. Issued 06/12/2017. Last accessed 06/16/2017.

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Appendix U

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

FDA NEWS RELEASE

For Immediate Release: June 8th, 2017

FDA requests removal of Opana ER for risks related to abuse

The U.S. Food and Drug Administration (FDA) requested that Endo Pharmaceuticals remove its opioid pain medication, reformulated Opana ER (oxymorphone hydrochloride), from the market. After careful consideration, the agency is seeking removal based on its concern that the benefits of the drug may no longer outweigh its risks. This is the first time the agency has taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse.

The FDA's decision is based on a review of all available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following the product's reformulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of HIV and hepatitis C, as well as cases of a serious blood disorder (thrombotic microangiopathy). This decision follows a March 2017 FDA advisory committee meeting where a group of independent experts voted 18-8 that the benefits of reformulated Opana ER no longer outweigh its risks.

Opana ER was first approved in 2006 for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In 2012, Endo replaced the original formulation of Opana ER with a new formulation intended to make the drug resistant to physical and chemical manipulation for abuse by snorting or injecting. While the product met the regulatory standards for approval, the FDA determined that the data did not show that the reformulation could be expected to meaningfully reduce abuse and declined the company's request to include labeling describing potentially abuse-deterrent properties for Opana ER. Now, with more information about the risks of the reformulated product, the agency is taking steps to remove the reformulated Opana ER from the market.

The FDA has requested that the company voluntarily remove reformulated Opana ER from the market. Should the company choose not to remove the product, the agency intends to take steps to formally require its removal by withdrawing approval. In the interim, the FDA is making health care professionals and others aware of the particularly serious risks associated with the abuse of this product.

The FDA will continue to examine the risk-benefit profile of all approved opioid analgesic products and take further actions as appropriate as a part of their response to this public health crisis.

FDA NEWS RELEASE

For Immediate Release: June 27th, 2017

FDA Tackles Drug Competition to Improve Patient Access

The FDA is taking two new, important steps to increase competition in the market for prescription drugs and facilitate entry of lower-cost alternatives. The agency published a list of off-patent, off-exclusivity branded drugs without approved generics, and also implemented, for the first time, a new policy to expedite the review of generic drug applications where competition is limited.

These actions are among the first taken under the agency's Drug Competition Action Plan, announced by FDA Commissioner Scott Gottlieb in late May.

To encourage generic drug development, the FDA posted a list of branded drugs that have no listed patents or exclusivities and for which the agency has yet to approve a generic drug application (known as an Abbreviated New Drug Application or ANDA). The agency also intends to expedite the review of any generic drug application for a product on this list to ensure that they come to market as expeditiously as possible. The FDA will continue to refine and update the list periodically to ensure continued transparency around drug categories where increased competition has the potential to provide significant benefit to patients.

The FDA is also announcing a change to its policy on how the agency prioritizes its review of generic drug applications. The FDA will expedite the review of generic drug applications until there are three approved generics for a given drug product. The agency is revising the policy based on data that indicate that consumers see significant price reductions when there are multiple FDA-approved generics available.

These actions follow closely the FDA's announcement of a public meeting to be held on July 18, 2017, to solicit input on places where the FDA's rules – including the standards and procedures related to generic

drug approvals – are being used in ways that may create obstacles to generic access, instead of ensuring the vigorous competition Congress intended.
These are the first of a series of steps the agency intends to take to help tackle this important issue. The agency will unveil additional aspects of this plan in the near future and will continue to communicate with the public as additional elements of this plan are implemented.
These actions reflect the administration's broader work to improve access to prescription drugs.

Safety Announcements

Bristol-Myers Squibb Voluntarily Recalls One Lot of Eliquis (apixaban) 5mg Tablets

[6/10/17] Bristol-Myers Squibb Company (NYSE: BMY) is voluntarily recalling one lot (#HN0063) of Eliquis 5mg tablets to the consumer level. This lot was distributed nationwide in the U.S. to wholesalers and retail pharmacies in February 2017. Bristol-Myers Squibb is taking this precautionary measure based on a customer complaint that a bottle labeled as Eliquis 5mg was found to contain Eliquis 2.5mg tablets.
Patients should not stop taking Eliquis without consulting with their physician. Patients who are prescribed Eliquis 5mg for an irregular heartbeat (atrial fibrillation) and take an Eliquis 2.5mg tablet instead, particularly for a prolonged period, would have an increased probability of stroke or death. For patients with Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), underdosing of the drug could lead to an increased risk of a growing or moving blood clot. Should that occur, it could be life-threatening or reversible depending on the severity and location of the blood clot. To date, there have not been any reports of injuries or illnesses related to this issue.
Eliquis tablets are indicated to reduce the risk of stroke and blood clots in people who have atrial fibrillation; it also treats blood clots in the veins of legs or lungs as well as reduces the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery. Eliquis 5mg tablets are packaged in 60-count bottles, lot HN0063, Exp 09/2019, NDC 0003-0894-21. The recalled lot was distributed Nationwide in the U.S. to wholesalers and retail pharmacies in February 2017.
There are distinct visible differences between the two tablet strengths including colors, size and markings that distinguish the 2.5mg and 5mg tablets and decrease the likelihood of an incorrect dose. The 2.5mg presentation is a yellow, round, biconvex, film-coated tablet with "893" debossed on one side and "2½" on the other side. The 5mg presentation is a pink, oval, biconvex, film-coated tablet with "894" debossed on one side and "5" on the other side.
Patient safety is the first priority. Bristol-Myers Squibb has notified wholesalers and pharmacies to arrange for return and replacement of any recalled product. Consumers that have product being recalled (Lot #HN0063) should contact their physician and call the Bristol-Myers Squibb Customer Information Center at 1-800-332-2056, Monday – Friday, from 8 AM – 8 PM EST or visit BMS.com for more information. See Eliquis U.S. Full Prescribing Information, including Boxed Warnings .
This recall is being conducted with the knowledge of the U.S. Food and Drug Administration. Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax. Consumers should contact their physician or healthcare provider if they have experienced any problems that may be related to taking this drug product.
They should complete and submit the report online: www.fda.gov/medwatch/report.htm. Regular Mail or Fax: The form can be downloaded from: www.fda.gov/MedWatch/getforms.htm or they can call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Safety Announcements

Topical Products by Phillips Company: Recall - Due to Concerns of Manufacturing Practices

[6/14/17] Phillips Company is voluntarily recalling all lots of Tetrastem, Diabecline, Tetracycline-ABC, VenomX, Acneen, StaphWash, StringMed, NoPain and LidoMed distributed by Phillips Company, with business offices located in Sun City, Arizona, to the retail level. The products are being recalled after an FDA inspection found significant manufacturing practices that calls into question the safety, identity, strength, quality and purity of unexpired drug products made at the firm during the past three years.
Manufacturing practices that are not in adequate control represent the possibility of risk being introduced into the manufacturing process in decreased quality and consistency of the product. These may have an impact on the safety and efficacy of the product posing a risk to patients. To date, no adverse events have been reported.

BACKGROUND: The topical antibiotic products are intended for treatment of minor cuts, scrapes and burns; or as skin cleansers or hair-growth promoters. All products are distributed in 5mL dropper bottles for topical application. The expiration date is printed on the label on the bottle. Products were distributed nationwide as wholesale products.
RECOMMENDATION: Phillips Company is notifying its distributors and customers by issuance of recall letters, and is arranging for return of all recalled products. Consumers/distributors/retailers that have a product which is being recalled should stop using the product and return any unused and unexpired products to the manufacturer. Consumers with questions regarding this recall can contact Phillips Company by e-mail (hp@valliant.net).
Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- They should complete and submit the report online: www.fda.gov/MedWatch/report
- They can download the form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Safety Announcements

Fagron Sterile Services Issues Voluntary Nationwide Recall of Succinylcholine Chloride Due to Potential For Lack of Sterility Assurance

[6-23-2017] Fagron Sterile Services is voluntarily recalling three (3) lots of Succinylcholine Chloride 20mg/mL 5mL syringe to the hospital/clinic level. The secondary recall of product manufactured by Hospira Inc., a Pfizer company, and repacked by Fagron Sterile Services is due to microbial growth detected during a routine simulation of Hospira's manufacturing process, which represents the potential introduction of microorganisms into the product. To date, there have been no reports of adverse events. This secondary recall is being conducted as result of the recall initiated by the manufacturer on June 15, 2017
Per Hospira, in the event that impacted product is administered to a patient, there is a reasonable probability that the patient may experience adverse events ranging from fever, chills and malaise, to severe adverse events including systemic invasive mycoses or systemic bacterial sepsis. The possibility of a breach in sterility assurance in distributed product, while remote, cannot be eliminated. No microorganisms have been confirmed in any Fagron Sterile Services lot. To date, Fagron Sterile Services has not received reports of any adverse events associated with this issue.
Succinylcholine Chloride Injection is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation and is repacked by Fagron Sterile Services into 5mL doses of Succinylcholine Chloride 20mg/mL. The impacted Succinylcholine Chloride 20mg/mL lots include the following:

Lot	Beyond-Use Date
C274-000000331	08/30/2017
C274-000001274	09/07/2017
C274-000001326	09/14/2017

The impacted lots were distributed nationwide directly to hospitals and surgical clinics.
Fagron Sterile Services has notified its direct customers by telephone and is arranging for return and replacement of all recalled products. Hospitals or surgical clinics that have received impacted product which is being recalled, should immediately examine stock and discontinue dispensing. They should promptly contact Stericycle to arrange product return at 1-888-628-0728, from Monday to Friday, 8:00am to 5:00pm EDT for instructions on how to return impacted product.
Consumers with questions regarding this recall can contact Fagron Sterile Services by phone at 1-877-405-8066 M-F 8:00am – 5:00pm CDT. Consumers should contact their physician or healthcare provider if they have experienced any problems that may be related to taking or using this drug product.
Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online:** www.fda.gov/medwatch/report.htm
- **Regular Mail or Fax:** They can download the form from www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

Current Drug Shortages Index (as of June 28th, 2017):

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

Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Bleomycin Sulfate for Injection	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cromolyn Sodium Inhalation Solution, USP	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Dihydroergotamine Mesylate Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Epinephrine Injection	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Indigotindisulfonate Sodium (Indigo Carmine) Injection	***Currently in Shortage***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Mecasermin [rDNA origin] (Increlex) Injection	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methylprednisolone Sodium Succinate for Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nitrous Oxide, Gas	***Currently in Shortage***
Pantoprazole (Protonix) Powder for Injection	***Currently in Shortage***
Penicillin G Benzathine (Bicillin L-A) Injection	***Currently in Shortage***
Penicillin G Benzathine and Penicillin G Procaine (Bicillin C-R) Injection	***Currently in Shortage***
Penicillin G Procaine Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Rocuronium Bromide Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine (Transderm Scop) Transdermal System Patch	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***

Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***
Tolmetin Sodium Tablets, USP	***Currently in Shortage***