Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
July 11, 2018
4:00pm

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

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review (DUR) Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for DUR Board Meeting – July 11, 2018

DATE: June 28, 2018

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

Enclosed are the following items related to the 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

Action Item – Update on Medication Coverage Authorization Unit/SoonerCare Opioid Initiative Update – Appendix B

Action Item – Vote to Prior Authorize Crysvita® (Burosumab-twza) – Appendix C

Action Item – Vote to Prior Authorize Imfinzi® (Durvalumab) and to Update the Current Lung Cancer Medications Prior Authorization Criteria – Appendix D

Action Item – Vote to Prior Authorize Erleada™ (Apalutamide) and Yonsa® (Abiraterone) – Appendix E

Action Item – Vote to Prior Authorize Cotempla XR-ODT™ [Methylphenidate Extended-Release (ER) Orally Disintegrating Tablet (ODT)], Mydayis® (Amphetamine/Dextroamphetamine ER Capsule), and Adzenys ER™ (Amphetamine ER Suspension) – Appendix F

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

Action Item – Annual Review of Atopic Dermatitis (AD) Medications – Appendix H

Action Item – Annual Review of Botulinum Toxins – Appendix I

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

30-Day Notice to Prior Authorize Jynarque™ (Tolvaptan) – Appendix K

Annual Review of Vimizim® (Elosulfase Alfa) – Appendix L

Annual Review of Brineura® (Cerliponase Alfa) – Appendix M

Annual Review of Radicava® (Edaravone) – Appendix N

Industry News and Updates – Appendix O

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – July 11, 2018 @ 4:00p.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 13, 2018 DUR Minutes – Vote
B. June 13, 2018 DUR Recommendations Memorandum

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

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

A. Medication Coverage Activity for June 2018
B. Pharmacy Help Desk Activity for June 2018
C. SoonerCare Opioid Initiative Update – Vote

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

5. Action Item – Vote to Prior Authorize Crysvita® (Burosumab-twza) – See Appendix C

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

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

6. Action Item – Vote to Prior Authorize Imfinzi® (Durvalumab) and to Update the Current Lung Cancer Medications Prior Authorization Criteria – See Appendix D

A. Introduction
B. Recommendations

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

7. Action Item – Vote to Prior Authorize Erleada™ (Apalutamide) and Yonsa® (Abiraterone) – See Appendix E

A. Introduction
B. Recommendations

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

8. Action Item – Vote to Prior Authorize Cotempla XR-ODT™ [Methylphenidate Extended-Release (ER) Orally Disintegrating Tablet (ODT)], Mydayis® (Amphetamine/Dextroamphetamine ER Capsule), and Adzenys ER™ (Amphetamine ER Suspension) – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

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

A. Introduction
B. College of Pharmacy Recommendations

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

10. Action Item – Annual Review of Atopic Dermatitis (AD) Medications – See Appendix H

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

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

11. Action Item – Annual Review of Botulinum Toxins – See Appendix I

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

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

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

A. Current Prior Authorization Criteria
B. Utilization of Opioid Analgesics and MAT Medications
C. Prior Authorization of Opioid Analgesics and MAT Medications
D. Market News and Updates
E. Apadaz® (Benzhydrocodone/APAP Tablets) Product Summary
F. Lucemyra™ (Lofexidine Tablets) Product Summary
G. Sublocade™ [Buprenorphine ER Injection] Product Summary
H. College of Pharmacy Recommendations
I. Utilization Details of Opioid Analgesics
J. Utilization Details of MAT Medications

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

13. 30-Day Notice to Prior Authorize Jynarque™ (Tolvaptan) – See Appendix K

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

Non-Presentation; Questions Only:

14. Annual Review of Vimizim® (Elosulfase Alfa) – See Appendix L

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Vimizim® (Elosulfase Alfa)
D. Prior Authorization of Vimizim® (Elosulfase Alfa)
E. College of Pharmacy Recommendations

Non-Presentation; Questions Only:

15. Annual Review of Brineura® (Cerliponase Alfa) – See Appendix M

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

Non-Presentation; Questions Only:

16. Annual Review of Radicava® (Edaravone) – See Appendix N

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

Non-Presentation; Questions Only:

17. Industry News and Updates – See Appendix O

A. Introduction
B. News and Updates

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

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

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

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

No meeting scheduled for August.

A. Antihyperlipidemics
B. Fabrazyme® (Agalsidase Beta)
C. Growth Hormone
D. Butalbital Medications
E. Synagis® (Palivizumab)
F. Breast Cancer Medications
G. Sickle Cell Medications

**Future business subject to change.*

20. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF JUNE 13, 2018

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

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

OTHERS PRESENT:		
Dr. Kenneth Berry, Alkermes	Dr. Michael Feld, Neos	Christy Heiner, Rhodes
Kristin Pareja, Otsuka	Audrey Rattan, Alkermes	Rhonda Clark, Indivior
Jane Stephen, Amgen	Nima Nabaui, Novo Nordisk	Maria Agapova, Teva
Gwendolyn Caldwell, PhRMA	Erica Brumleve, GSK	Scott Poole, Intersect ENT
Dan Doyle, Trividia	Toby Thompson, Pfizer	Ron Cain, Pfizer
Jim Chapman, AbbVie	Marc Parker, Sunovion	Amber Schrantz, Lilly
Brad Willie, Neurocrine	Deron Grothe, Teva	Chris Bryant, Teva
Brian Buckles, Takeda	Jose Montoya, Takeda	Mary Blasi, Intersect ENT
Paul Sparks, Amicus Therapeutics	Mark Kaiser, Otsuka	Kristi Kemp, Allergan
Doug Wood, Viiv	Aaron Shaw, Boehringer Ingelheim	Ron Schnare, Shire
Mai Doung, Novartis	Cris Valladares, Celgene	Dr. James Gilbert, Allergan

PRESENT FOR PUBLIC COMMENT:	
Dr. Michael Feld	Neos
Dr. Kenneth Berry	Alkermes
Christy Heiner	Rhodes
Kristin Pareja	Otsuka
Maria Agapova	Teva
Dr. James Gilbert	Allergan

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: MARIA AGAPOVA
2B: AGENDA ITEM NO. 14 SPEAKER: DR. MICHAEL FELD
2C: AGENDA ITEM NO. 14 SPEAKER: CHRISTY HEINER
2D: AGENDA ITEM NO. 17 SPEAKER: DR. KENNETH BERRY
2E: AGENDA ITEM NO. 17 SPEAKER: KRISTIN PAREJA
2F: AGENDA ITEM NO. 17 SPEAKER: DR. JAMES GILBERT

ACTION: NONE REQUIRED

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

3A: APRIL 11, 2018 DUR MINUTES – VOTE
3B: APRIL 11, 2018 DUR RECOMMENDATIONS MEMORANDUM
3C: MAY 9, 2018 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Cothran

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/ADHD PRESCRIPTION USE IN REPRODUCTIVE-AGED WOMEN**

4A: MEDICATION COVERAGE ACTIVITY FOR MAY 2018
4B: PHARMACY HELP DESK ACTIVITY FOR MAY 2018
4C: ADHD PRESCRIPTION USE IN REPRODUCTIVE-AGED WOMEN

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE CLENPIQ™ (SODIUM PICOSULFATE/ MAGNESIUM OXIDE/ANHYDROUS CITRIC ACID)**

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Ms. Varalli-Claypool moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE OTIPRIO® (CIPROFLOXACIN OTIC SUSPENSION)
6A: INTRODUCTION
6B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Anderson moved to approve; seconded by Dr. Preslar
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE ADMELOG® (INSULIN LISPRO), BYDUREON® BCISE™ (EXENATIDE EXTENDED-RELEASE AUTOINJECTOR PEN), FIASP® (INSULIN ASPART), HUMULIN® R U-500 VIALS (INSULIN HUMAN 500 UNITS/ML), OZEMPIC® (SEMAGLUTIDE), STEGLATRO™ (ERTUGLIFLOZIN), SEGLUROMET™ (ERTUGLIFLOZIN/METFORMIN), AND STEGLUJAN™ (ERTUGLIFLOZIN/SITAGLIPTIN)
7A: INTRODUCTION
7B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Hardzog-Britt moved to approve; seconded by Dr. Preslar
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO UPDATE THE PRIOR AUTHORIZATION CRITERIA FOR TAZORAC® (TAZAROTENE CREAM AND GEL)
8A: INTRODUCTION
8B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Adams
Dr. Preslar moved to approve; seconded by Ms. Varalli-Claypool
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE PREXXARTAN® (VALSARTAN ORAL SOLUTION), TEKTURNA® (ALISKIREN ORAL PELLETS), AND CAROSPIR® (SPIRONOLACTONE ORAL SUSPENSION)
9A: INTRODUCTION
9B: MARKET NEWS AND UPDATES
9C: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
Dr. Harrell moved to approve; seconded by Dr. Anderson
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: VOTE TO PRIOR AUTHORIZE BENZNIDAZOLE
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: ANNUAL REVIEW OF LUNG CANCER MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE IMFINZI® (DURVALUMAB) AND TO UPDATE THE CURRENT PRIOR AUTHORIZATION CRITERIA
11A: INTRODUCTION
11B: CURRENT PRIOR AUTHORIZATION CRITERIA
11C: UTILIZATION OF LUNG CANCER MEDICATIONS

11D: PRIOR AUTHORIZATION OF LUNG CANCER MEDICATIONS
11E: MARKET NEWS AND UPDATES
11F: IMFINZI® (DURVALUMAB) PRODUCT SUMMARY
11G: RECOMMENDATIONS
11H: UNTILIZATION DETAILS OF LUNG CANCER MEDICATIONS
Materials included in agenda packet; presented by Dr. Medina
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: ANNUAL REVIEW OF PROSTATE CANCER MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ERLEADA™ (APALUTAMIDE) AND YONSA® (ABIRATERONE)
12A: INTRODUCTION
12B: CURRENT PRIOR AUTORIZATION CRITERIA
12C: UTILIZATION OF PROSTATE CANCER MEDICATIONS
12D: PRIOR AUTHORIZATION OF PROSTATE CANCER MEDICATIONS
12E: MARKET NEWS AND UPDATES
12F: PRODUCT SUMMARIES
12G: RECOMMENDATIONS
12H: UTILIZATION DETAILS OF PROSTATE CANCER MEDICATIONS
Materials included in agenda packet; presented by Dr. Medina
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF VESICULAR MONOAMINE TRANSPORTER 2 (VMAT2) INHIBITOR MEDICATIONS AND VOTE TO PRIOR AUTHORIZE AUSTEDO® (DEUTETRABENAZINE) FOR TARDIVE DYSKINESIA
13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF VMAT2 INHIBITOR MEDICATIONS
13C: PRIOR AUTHORIZATION OF VMAT2 INHIBITOR MEDICATIONS
13D: MARKET NEWS AND UPDATES
13E: VMAT2 INHIBITOR COST COMPARISON
13F: COLLEGE OF PHARMACY RECOMMENDATIONS
13G: UTILIZATION DETAILS OF VMAT2 INHIBITOR MEDICATIONS
Materials included in agenda packet; presented by Dr. Abbott
Dr. Anderson moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 14: ANNUAL REVIEW OF ADHD AND NARCOLEPSY MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE COTEMPLA XR-ODT™ [METHYLPHENIDATE EXTENDED-RELEASE (ER) ORALLY DISINTEGRATING TABLET (ODT)], MYDAYIS® (AMPHETAMINE/DEXTROAMPHETAMINE ER CAPSULE), AND ADZENYS ER™ (AMPHETAMINE ER SUSPENSION)
14A: CURRENT PRIOR AUTHORIZATION CRITERIA
14B: UTILIZATION OF ADHD AND NARCOLEPSY MEDICATIONS
14C: PRIOR AUTHORIZATION OF ADHD AND NARCOLEPSY MEDICATIONS
14D: MEDICAID DRUG REBATE PROGRAM
14E: MARKET NEWS AND UPDATES
14F: COTEMPLA XR-ODT™ (METHYLPHENIDATE ER ODT) PRODUCT SUMMARY
14G: MYDAYIS® (AMPHETAMINE/DEXTROAMPHETAMINE ER CAPSULE) PRODUCT SUMMARY
14H: ADZENYS ER™ (AMPHETAMINE ER SUSPENSION) PRODUCT SUMMARY
14I: COLLEGE OF PHARMACY RECOMMENDATIONS
14J: UTILIZATION DETAILS OF ADHD AND NARCOLEPSY MEDICATIONS
Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: **30-DAY NOTICE TO PRIOR AUTHORIZE CRYSVITA® (BUROSUMAB-TWZA)**

15A: INTRODUCTION
15B: MARKET NEWS AND UPDATES
15C: CRYSVITA® (BUROSUMAB-TWZA) PRODUCT SUMMARY
15D: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: **ANNUAL REVIEW OF VARIOUS SPECIAL FORMULATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE BACLOFEN 5MG TABLET, ESOMEP-EZS™ (ESOMEPRAZOLE KIT), LYRICA® CR (PREGABALIN EXTENDED-RELEASE), RESTASIS MULTIDOSE® (CYCLOSPORINE 0.05% OPHTHALMIC EMULSION), SINUVA™ (MOMETASONE FUROATE SINUS IMPLANT), XEPI™ (OZENOXACIN 1% CREAM), XHANCE™ (FLUTICASONE PROPIONATE NASAL SPRAY), AND ZTLIDO™ (LIDOCAINE 1.8% TOPICAL SYSTEM)**

16A: INTRODUCTION
16B: CURRENT PRIOR AUTHORIZATION CRITERIA
16C: UTILIZATION OF SPECIAL FORMULATIONS
16D: PRIOR AUTHORIZATION OF SPECIAL FORMULATIONS
16E: BACLOFEN 5MG TABLET PRODUCT SUMMARY
16F: ESOMEP-EZS™ (ESOMEPRAZOLE KIT) PRODUCT SUMMARY
16G: LYRICA® CR (PREGABALIN EXTENDED-RELEASE) PRODUCT SUMMARY
16H: RESTASIS MULTIDOSE® (CYCLOSPORINE 0.05% OPHTHALMIC EMULSION) PRODUCT SUMMARY
16I: SINUVA™ (MOMETASONE FUROATE SINUS IMPLANT) PRODUCT SUMMARY
16J: XEPI™ (OZENOXACIN 1% CREAM) PRODUCT SUMMARY
16K: XHANCE™ (FLUTICASONE PROPIONATE NASAL SPRAY) PRODUCT SUMMARY
16L: ZTLIDO™ (LIDOCAINE 1.8% TOPICAL SYSTEM) PRODUCT SUMMARY
16M: COLLEGE OF PHARMACY RECOMMENDATIONS
16N: UTILIZATION DETAILS OF SPECIAL FORMULATIONS

Materials included in agenda packet; presented by Dr. Chandler

ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: **ANNUAL REVIEW OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS**

17A: CURRENT PRIOR AUTHORIZATION CRITERIA
17B: UTILIZATION OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS
17C: PRIOR AUTHORIZATION OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS
17D: MEDICAID DRUG REBATE PROGRAM
17E: MARKET NEWS AND UPDATES
17F: COLLEGE OF PHARMACY RECOMMENDATIONS
17G: UTILIZATION DETAILS OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS

Materials included in agenda packet; presented by Dr. Nawaz

ACTION: NONE REQUIRED

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

18A: INTRODUCTION
18B: NEWS AND UPDATES

Materials included in agenda packet; Non-presentation; Questions only

ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: **U.S. FOOD AND DRUG ADMINISTRATION (FDA) AND DRUG ENFORCEMENT ADMINISTRATION (DEA) UPDATES**

Materials included in agenda packet; presented by Dr. Cothran

ACTION: NONE REQUIRED

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

20A: JYNARQUE™ (TOLVAPTAN)

20B: OPIOID ANALGESICS AND OPIOID MEDICATION ASSISTED TREATMENT (MAT) MEDICATIONS

20C: ATOPIC DERMATITIS MEDICATIONS

20D: BRINEURA® (CERLIPONASE ALFA)

20E: RADICAVA® (EDARAVONE)

20F: VIMIZIM® (ELOSULFASE ALFA)

20G: BOTULINUM TOXINS

FUTURE BUSINESS SUBJECT TO CHANGE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: **NONE REQUIRED**

AGENDA ITEM NO. 21: **ADJOURNMENT**

The meeting was adjourned at 5:45pm.

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

Memorandum

Date: June 14, 2018

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

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of June 13, 2018

Recommendation 1: ADHD Prescription Use in Reproductive-Aged Women

NO ACTION REQUIRED.

Little information is known regarding the risks of attention-deficit/hyperactivity disorder (ADHD) medication use in pregnancy. Given that a large percentage of births are unplanned, ADHD medication use in females of reproductive age could result in early pregnancy exposure, a critical period for fetal development. The College of Pharmacy recommends education via letter or newsletter for members, prescribers, and pharmacies who are or have female members of reproductive age utilizing ADHD medications. Education should include linking providers and members to resources such as the Centers for Disease Control and Prevention's (CDC) *Treating for Two: Safer Medication Use in Pregnancy* initiative. The College of Pharmacy will continue to monitor appropriate stimulant use in this population and make recommendations to the DUR Board where appropriate.

Recommendation 2: Vote to Prior Authorize Clenpiq™ (Sodium Picosulfate/ Magnesium Oxide/Anhydrous Citric Acid)

MOTION CARRIED by unanimous approval.

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

Clenpiq™, 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 why 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 3: Vote to Prior Authorize Otiprio® (Ciprofloxacin Otic Suspension)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the placement of Otiprio® (ciprofloxacin 6% otic suspension) into the Special Prior Authorization (PA) Tier of the Otic Anti-Infective Medications Product Based Prior Authorization (PBPA) category with the following criteria:

Otiprio® (Ciprofloxacin 6% Otic Suspension) Approval Criteria:

1. An FDA approved indication of one of the following:
   a. For the treatment of bilateral otitis media with effusion in members undergoing tympanostomy tube placement; or
   b. For the treatment of acute otitis externa due to *Pseudomonas aeruginosa (P. aeruginosa) or Staphylococcus aureus (S. aureus);* and
2. Member must be 6 months of age or older; and
3. Otiprio® must be administered by a health care professional; and
4. A patient-specific, clinically significant reason why appropriate lower tiered otic anti-infective medications cannot be used; and
5. A quantity limit of 1 vial per treatment course will apply.

Otic Anti-Infective Medications		
Tier-1	**Tier-2**	**Special PA**
acetic acid (VoSol®, Acetasol®)	ciprofloxacin 0.2% (Cetraxal®)	acetic acid/HC (Acetasol® HC, VoSol® HC)
ciprofloxacin/dexamethasone (Ciprodex®)	ciprofloxacin/fluocinolone (Otovel®)	**ciprofloxacin 6% (Otiprio®)**
ciprofloxacin/HC (Cipro® HC)	finafloxacin (Xtoro™)	
neomycin/colistin/HC/ thonzonium (Coly-Mycin® S)	neomycin/polymyxin B/HC (Cortisporin®, Pediotic®)	
	ofloxacin (Floxin® Otic)	

PA = prior authorization; HC = hydrocortisone
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendation 4: Vote to Prior Authorize Admelog® (Insulin Lispro), Bydureon® BCise™ (Exenatide Extended-Release Autoinjector Pen), Fiasp® (Insulin Aspart), Humulin® R U-500 Vials (Insulin Human 500 Units/mL), Ozempic® (Semaglutide), Steglatro™ (Ertugliflozin), Segluromet™ (Ertugliflozin/ Metformin), and Steglujan™ (Ertugliflozin/Sitagliptin)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Admelog® (insulin lispro), Fiasp® (insulin aspart), and Humulin® R U-500 vials (insulin human 500 units/mL) with the following criteria:

Admelog® (Insulin Lispro) Approval Criteria:

1. An FDA approved diagnosis of diabetes mellitus; and
2. A patient-specific, clinically significant reason why the member cannot use Humalog® (insulin lispro) must be provided.

Fiasp® (Insulin Aspart) Approval Criteria:

1. An FDA approved diagnosis of diabetes mellitus; and
2. A patient-specific, clinically significant reason why the member cannot use NovoLog® (insulin aspart) must be provided.

Humulin® R U-500 Vials (Insulin Human 500 Units/mL) Approval Criteria:

1. An FDA approved diagnosis of diabetes mellitus; and
2. A patient-specific, clinically significant reason why the member cannot use the Humulin® R U-500 KwikPen® (insulin human 500 units/mL), which is available without prior authorization, must be provided.

The College of Pharmacy also recommends the following changes to the Diabetes Medications Product Based Prior Authorization (PBPA) criteria and tier chart based on net costs after rebates:

1. Add Bydureon® BCise™ [exenatide extended-release (ER) autoinjector pen] into the Special Prior Authorization (PA) Tier.
    a. Authorization of Bydureon® BCise™ will require tier trials be met, and a patient-specific, clinically significant reason why the member cannot use other available formulations of exenatide must be provided. Current Special PA criteria will apply.
2. Place Ozempic® (semaglutide), Steglatro™ (ertugliflozin), Segluromet™ (ertugliflozin/metformin), and Steglujan™ (ertugliflozin/sitagliptin) into Tier-3. Current Tier-3 criteria will apply.
3. Add a patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) with an alternative glucagon-like peptide-1 (GLP-1) receptor agonist to the Soliqua® (insulin glargine/lixisenatide) criteria.
4. Add a patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) with Victoza® (liraglutide) to the Xultophy® (insulin degludec/ liraglutide) criteria.

5. Add a patient-specific, clinically significant reason why the member cannot take the immediate-release formulation to the Invokamet® XR (canagliflozin/metformin ER) and Jentadueto® XR (linagliptin/metformin ER) criteria.

The recommended changes are shown in red in the following criteria and tier chart:

Diabetes Medications Special Prior Authorization (PA) Approval Criteria:

1. Member must be currently stabilized on the requested product or have attempted at least three other categories of Tier-2 or Tier-3 medications, or have a documented clinical reason why the requested product is necessary for the member; and
2. Use of Invokamet® XR [canagliflozin/metformin extended-release (ER)] or Jentadueto® XR (linagliptin/metformin ER) will require a patient-specific, clinically significant reason why the member cannot take the immediate-release formulation(s); or
3. Use of Bydureon® BCise™ (exenatide ER autoinjector pen) will require tier trials be met, and a patient-specific, clinically significant reason why the member cannot use other available formulations of exenatide must be provided.

Soliqua® 100/33 (Insulin Glargine/Lixisenatide) Approval Criteria:

1. An FDA approved diagnosis of type 2 diabetes mellitus; and
2. A patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) with an alternative glucagon-like peptide-1 (GLP-1) receptor agonist must be provided; and
3. Current Tier-3 criteria will apply.

Xultophy® 100/3.6 (Insulin Degludec/Liraglutide) Approval Criteria:

1. An FDA approved diagnosis of type 2 diabetes mellitus; and
2. A patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) with Victoza® (liraglutide) must be provided; and
3. Current Tier-3 criteria will apply.

Diabetes Medications*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Alpha-Glucosidase Inhibitors acarbose (Precose®)	**DPP-4 Inhibitors** saxagliptin (Onglyza®) saxagliptin/metformin (Kombiglyze®) sitagliptin (Januvia®) sitagliptin/metformin (Janumet®) sitagliptin/metformin ER (Janumet XR®)	**Alpha-Glucosidase Inhibitors** miglitol (Glyset®)	**Amylinomimetics** pramlintide (Symlin®)
Biguanides metformin (Glucophage®) metformin SR (Glucophage XR®) metformin/glipizide (Metaglip®) metformin/glyburide (Glucovance®)	**Glinides** nateglinide (Starlix®) repaglinide/metformin (Prandimet®)	**Dopamine Agonists** bromocriptine (Cycloset®)	**Biguanides** metformin ER (Fortamet®, Glumetza®) metformin solution (Riomet®)
Glinides repaglinide (Prandin®)		**DPP-4 Inhibitors** alogliptin (Nesina®) alogliptin/metformin (Kazano®) alogliptin/pioglitazone (Oseni®) linagliptin (Tradjenta®) linagliptin/metformin (Jentadueto®)	**DPP-4 Inhibitors** linagliptin/metformin ER (Jentadueto® XR)
		GLP-1 Agonists albiglutide (Tanzeum®) dulaglutide (Trulicity®) lixisenatide (Adlyxin™) **semaglutide (Ozempic®)**	**GLP-1 Agonists** **exenatide ER autoinjector pen (Bydureon® BCise™)**

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

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

Recommendation 5: Vote to Update the Prior Authorization Criteria for Tazorac® (Tazarotene Cream and Gel)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes noted in red to the current Tazorac® (tazarotene cream and gel) prior authorization criteria, based on current net costs:

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 0.1% cream will require a patient-specific, clinically significant reason why the member cannot use the other formulations of tazarotene (brand Tazorac® 0.05% cream, 0.05% gel, and 0.1% gel are preferred) ~~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
   b. Based on current net costs, Tazorac® 0.05% cream, 0.05% gel, and 0.1% gel will not require prior authorization for members 20 years of age or younger; and
5. A quantity limit of 60 grams per 30 days will apply.

Recommendation 6: Vote to Prior Authorize Prexxartan® (Valsartan Oral Solution), Tekturna® (Aliskiren Oral Pellets), and CaroSpir® (Spironolactone Oral Suspension)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Prexxartan® (valsartan oral solution), Tekturna® (aliskiren oral pellets), and CaroSpir® (spironolactone oral suspension) with the following criteria:

Prexxartan® (Valsartan Oral Solution) Approval Criteria:

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

Tekturna® (Aliskiren Oral Pellets) Approval Criteria:

1. An FDA approved indication; and
2. A recent trial, within the previous six months and at least four weeks in duration, of an angiotensin I converting enzyme inhibitor (ACEI) [or an angiotensin II receptor blocker (ARB) if previous trial of an ACEI] and a diuretic, used concomitantly at recommended doses, that did not yield adequate blood pressure control; and
3. Member must be 6 years of age or older; and
4. A patient-specific, clinically significant reason why the member cannot use Tekturna® tablets must be provided.

CaroSpir® (Spironolactone Oral Suspension) Approval Criteria:

1. An FDA approved indication; and
2. A patient-specific, clinically significant reason why the member cannot use spironolactone oral tablets must be provided.

Additionally, the College of Pharmacy recommends the following changes to the Antihypertensive Medication Product Based Prior Authorization (PBPA) category based on net costs:

1. Moving Cardizem® SR [diltiazem sustained-release (SR)], Verelan® [verapamil extended-release (ER) capsule], Capoten® (captopril), and Capozide® [captopril/ hydrochlorothiazide (HCTZ)] from Tier-1 to Tier-2. Current Tier-2 criteria will apply.
2. Moving Exforge® (amlodipine/valsartan) and Micardis® (telmisartan) from Tier-2 to Tier-1.

The recommended changes are shown in red in the following tier charts:

Angiotensin Converting Enzyme Inhibitors (ACEIs)		
Tier-1	**Tier-2**	**Special PA**
benazepril (Lotensin®)	**captopril (Capoten®)**	enalapril oral solution (Epaned®)
enalapril (Vasotec®)		lisinopril oral solution (Qbrelis®)
enalaprilat (Vasotec® IV)		
fosinopril (Monopril®)		
lisinopril (Prinivil®, Zestril®)		
moexipril (Univasc®)		
perindopril erbumine (Aceon®)		
quinapril (Accupril®)		
ramipril (Altace®)		
trandolapril (Mavik®)		

PA = prior authorization; IV = intravenous

Angiotensin Converting Enzyme Inhibitors (ACEIs)/ Hydrochlorothiazide (HCTZ) Combinations		
Tier-1	**Tier-2**	**Special PA**
benazepril/HCTZ (Lotensin® HCT)	**captopril/HCTZ (Capozide®)**	fosinopril/HCTZ (Monopril-HCT®)
enalapril/HCTZ (Vasoretic®)		
lisinopril/HCTZ (Prinzide®, Zestoretic®)		
moexipril/HCTZ (Uniretic®)		
quinapril/HCTZ (Accuretic®)		

PA = prior authorization

Angiotensin Receptor Blockers (ARBs) and ARB Combination Products		
Tier-1	**Tier-2**	**Tier-3**
irbesartan (Avapro®)	amlodipine/olmesartan (Azor®)	azilsartan (Edarbi®)
irbesartan/HCTZ (Avalide®)	amlodipine/valsartan/HCTZ (Exforge® HCT)	azilsartan/chlorthalidone (Edarbyclor®)
losartan (Cozaar®)	olmesartan (Benicar®)	candesartan (Atacand®)
losartan/HCTZ (Hyzaar®)	olmesartan/HCTZ (Benicar HCT®)	candesartan/HCTZ (Atacand® HCT)
telmisartan (Micardis®)	olmesartan/amlodipine/HCTZ (Tribenzor®)	eprosartan (Teveten®)
valsartan (Diovan®)		eprosartan/HCTZ (Teveten® HCT)
valsartan/amlodipine (Exforge®)		telmisartan/amlodipine (Twynsta®)
valsartan/HCTZ (Diovan HCT®)		telmisartan/HCTZ (Micardis® HCT)

HCTZ = hydrochlorothiazide

Calcium Channel Blockers (CCBs)		
Tier-1	**Tier-2**	**Special PA**
amlodipine (Norvasc®)	amlodipine/atorvastatin (Caduet®)	diltiazem CD 360mg (Cardizem® CD)
diltiazem (Cardizem®)	diltiazem LA (Cardizem® LA, Matzim® LA)	
diltiazem (Tiazac®, Taztia XT®)	**diltiazem SR (Cardizem® SR)**	
diltiazem CD (Cardizem® CD)*	isradipine (Dynacirc®, Dynacirc CR®)	
diltiazem ER (Cartia XT®, Diltia XT®)	nicardipine (Cardene® SR)	

Calcium Channel Blockers (CCBs)		
Tier-1	**Tier-2**	**Special PA**
diltiazem XR (Dilacor® XR)	nisoldipine (Sular®)	
felodipine (Plendil®)	verapamil (Covera-HS®)	
nicardipine (Cardene®)	verapamil ER (**Verelan®**, Verelan® PM)	
nifedipine (Adalat®, Procardia®)		
nifedipine ER (Adalat® CC)		
nifedipine ER		
nifedipine XL (Nifedical XL®, Procardia XL®)		
nimodipine (Nimotop®)		
verapamil (Calan®, Isoptin®)		
verapamil SR (Calan® SR, Isoptin® SR)		

PA = prior authorization; XR, XL, ER = extended-release; SR = sustained-release; LA = long-acting; CD = controlled-delivery
*All strengths other than 360mg.

Recommendation 7: Vote to Prior Authorize Benznidazole

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of benznidazole tablets with the following criteria:

Benznidazole Tablets Approval Criteria:

1. An FDA approved diagnosis of Chagas disease (American trypanosomiasis) caused by *Trypanosoma cruzi*; and
2. Benznidazole must be prescribed by or in consultation with an infectious disease specialist; and
3. Female members of reproductive potential must have a pregnancy test prior to treatment with benznidazole; and
4. Female members of reproductive potential must be willing to use effective contraception during treatment with benznidazole tablets and for 5 days after the last dose; and
5. Member must not have taken disulfiram within the last two weeks; and
6. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug. The approval duration will be for 60 days of therapy.

Recommendation 8: Annual Review of Lung Cancer Medications and 30-Day Notice to Prior Authorize Imfinzi® (Durvalumab) and to Update the Current Prior Authorization Criteria

NO ACTION REQUIRED.

Recommendation 9: Annual Review of Prostate Cancer Medications and 30-Day Notice to Prior Authorize Erleada™ (Apalutamide) and Yonsa® (Abiraterone)

NO ACTION REQUIRED.

Recommendation 10: Annual Review of Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor Medications and Vote to Prior Authorize Austedo® (Deutetrabenazine) for Tardive Dyskinesia

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Austedo® (deutetrabenazine) for tardive dyskinesia (TD) with the following criteria:

Austedo® (Deutetrabenazine) Approval Criteria [Tardive Dyskinesia Diagnosis]:

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. Austedo® 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 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. For members requiring doses of Austedo® above 24mg per day, who are using Austedo® concomitantly with other medications that are known to prolong the QTc interval [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] the prescriber must agree to assess the QTc interval before and after increasing the dose of Austedo® or other medications that are known to prolong the QTc interval; and
10. The member must not have congenital long QT syndrome or a history of cardiac arrhythmias; and
11. 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
12. Female members must not be pregnant or breastfeeding; and

13. Prescriber must document a baseline evaluation using the Abnormal Involuntary Movement Scale (AIMS); and
14. 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) or documentation of a positive clinical response to therapy.

The College of Pharmacy recommends the following changes to the current prior authorization criteria for Austedo® (deutetrabenazine) and Ingrezza® (valbenazine) as shown in red below:

Austedo® (Deutetrabenazine) Approval Criteria [Huntington's Disease Diagnosis]:

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. For members requiring doses of Austedo® above 24mg per day, who are using Austedo® concomitantly with other medications that are known to prolong the QTc interval [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] the prescriber must agree to assess the QTc interval before and after increasing the dose of Austedo® or other medications that are known to prolong the QTc interval; and
11. The member must not have congenital long QT syndrome or a history of cardiac arrhythmias; and
12. 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

13. 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.

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. The daily dose of Ingrezza® must not exceed 40mg per day for members with moderate or severe hepatic impairment (Child-Pugh score 7 to 15); and
9. The member must not have congenital long QT syndrome or a history of arrhythmias associated with a prolonged QT interval; and
10. Female members must not be pregnant or breastfeeding; and
11. Prescriber must document a baseline evaluation using the Abnormal Involuntary Movement Scale (AIMS); and
12. A quantity limit of one capsule per day will apply; and
13. 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) or documentation of a positive clinical response to therapy.

Recommendation 11: Annual Review of ADHD and Narcolepsy Medications and 30-Day Notice to Prior Authorize Cotempla XR-ODT™ [Methylphenidate Extended-Release (ER) Orally Disintegrating Tablet (ODT)], Mydayis® (Amphetamine/Dextroamphetamine ER Capsule), and Adzenys ER™ (Amphetamine ER Suspension)

NO ACTION REQUIRED.

Recommendation 12: 30-Day Notice to Prior Authorize Crysvita® (Burosumab-twza)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Various Special Formulations and 30-Day Notice to Prior Authorize Baclofen 5mg Tablet, Esomep-EZS™ (Esomeprazole Kit), Lyrica® CR (Pregabalin Extended-Release), Restasis MultiDose® (Cyclosporine 0.05% Ophthalmic Emulsion), Sinuva™ (Mometasone Furoate Sinus Implant), Xepi™ (Ozenoxacin 1% Cream), Xhance™ (Fluticasone Propionate Nasal Spray), and ZTlido™ (Lidocaine 1.8% Topical System)

NO ACTION REQUIRED.

Recommendation 14: Annual Review of Atypical Antipsychotic Medications

NO ACTION REQUIRED.

Recommendation 15: Industry News and Updates

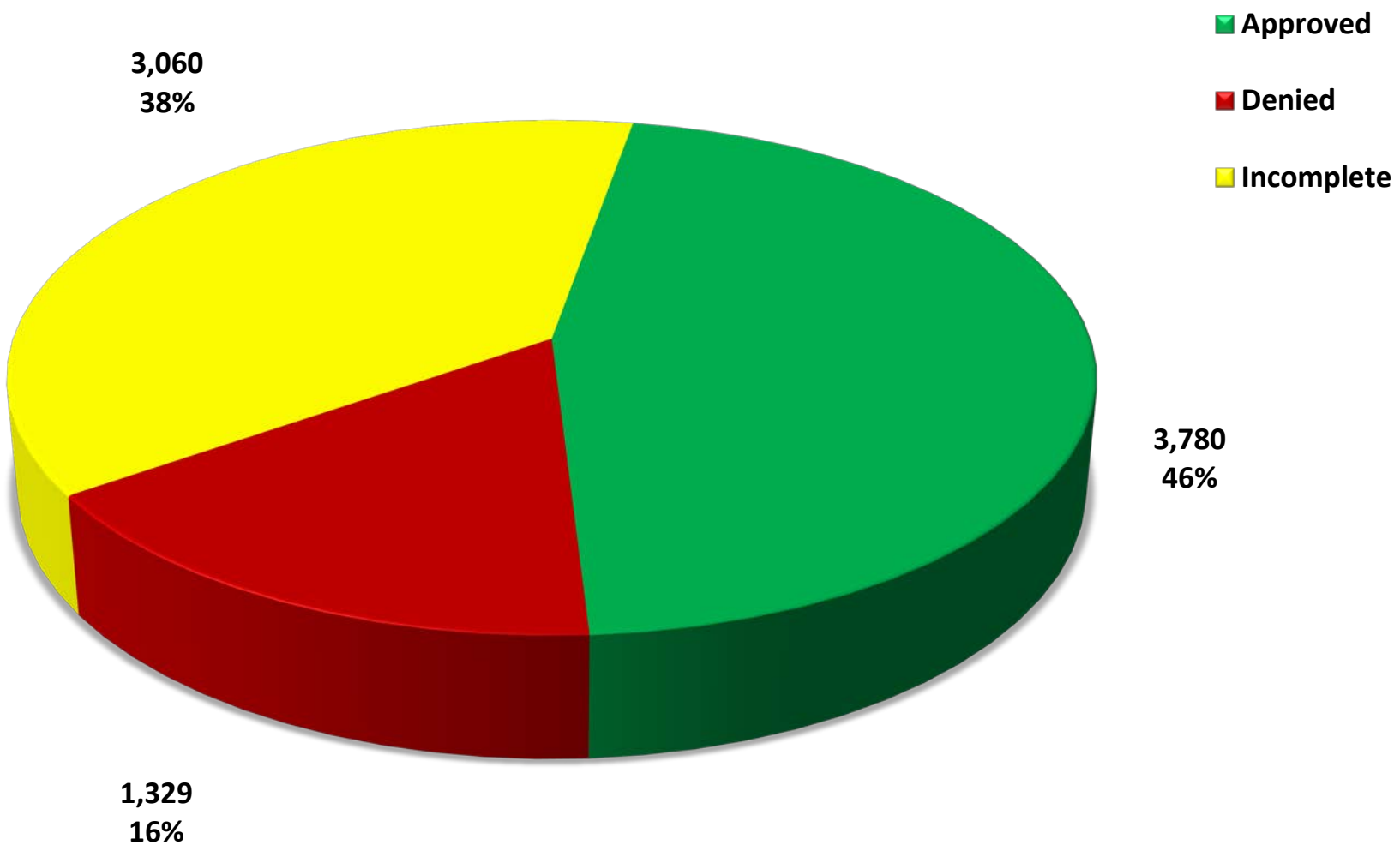
NO ACTION REQUIRED.

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

NO ACTION REQUIRED.

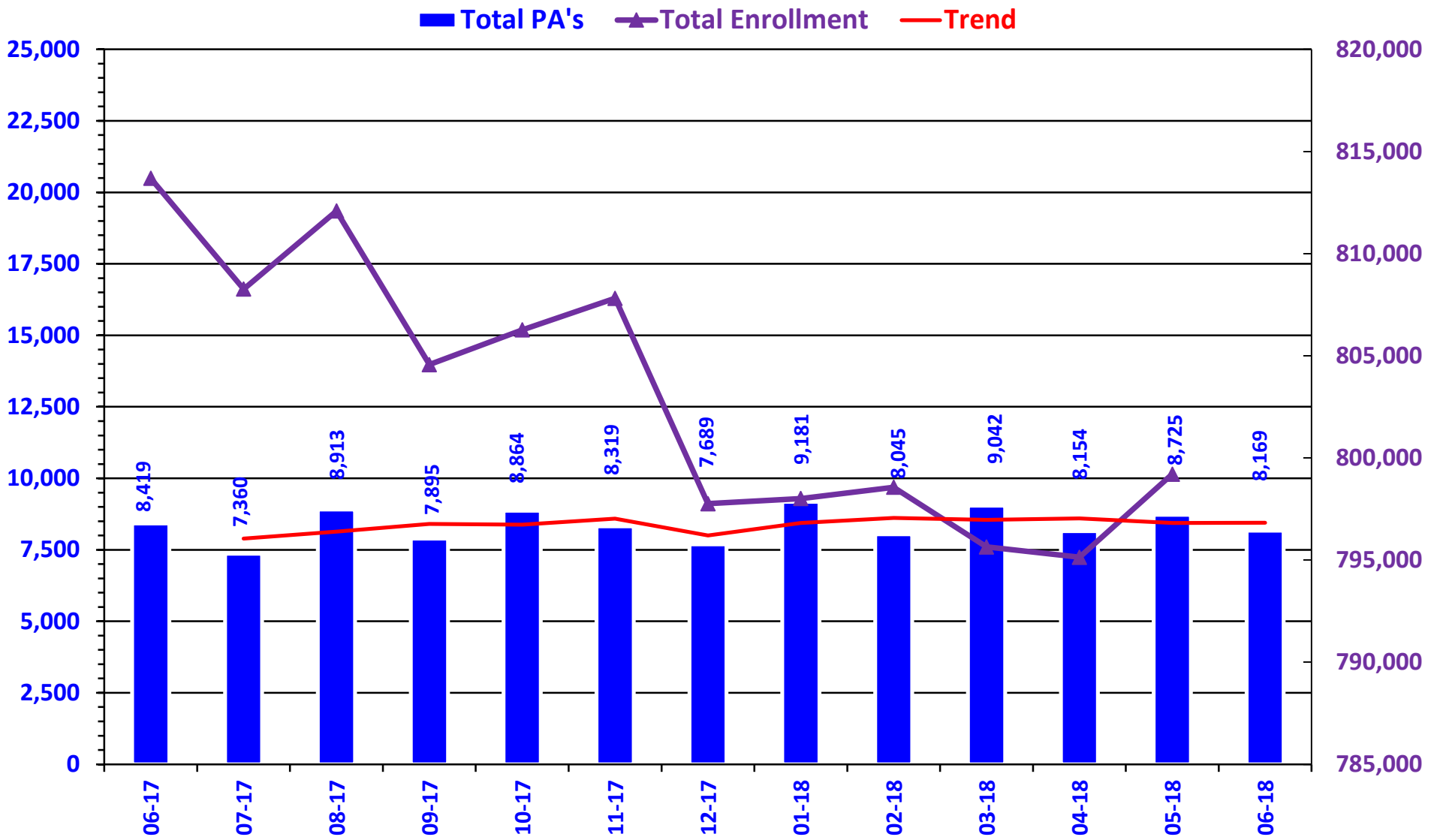
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: JUNE 2018



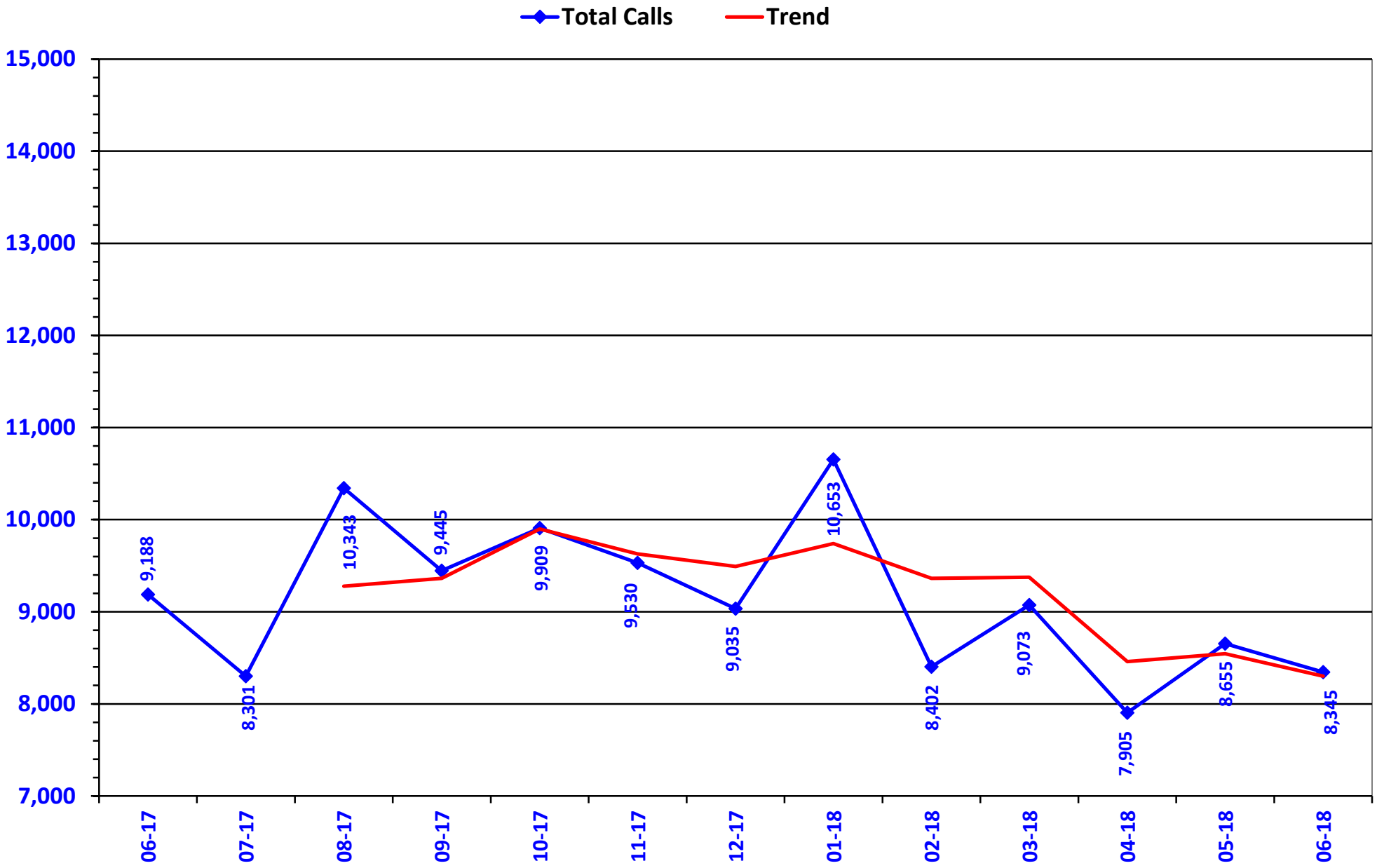
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: JUNE 2017 – JUNE 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
JUNE 2017 – JUNE 2018



Prior Authorization Activity

6/1/2018 Through 6/30/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	253	24	72	157	323
Analgesic - NonNarcotic	24	0	4	20	0
Analgesic - Narcotic	382	174	57	151	163
Angiotensin Receptor Antagonist	13	8	0	5	273
Antiasthma	65	17	21	27	231
Antibiotic	22	16	0	6	258
Anticonvulsant	116	46	17	53	306
Antidepressant	175	45	30	100	349
Antidiabetic	212	69	40	103	348
Antigout	18	9	5	4	291
Antihistamine	22	5	6	11	299
Antimigraine	44	5	11	28	231
Antineoplastic	86	63	10	13	153
Antiparasitic	23	5	2	16	8
Antiulcers	147	40	42	65	135
Anxiolytic	69	40	6	23	288
Atypical Antipsychotics	186	96	20	70	342
Biologics	119	70	16	33	311
Bladder Control	53	10	20	23	359
Blood Thinners	249	143	18	88	337
Botox	27	19	5	3	358
Buprenorphine Medications	398	282	14	102	76
Cardiovascular	97	39	12	46	319
Chronic Obstructive Pulmonary Disease	163	39	39	85	301
Constipation/Diarrhea Medications	151	18	54	79	210
Contraceptive	22	17	1	4	357
Dermatological	151	23	48	80	243
Diabetic Supplies	473	277	20	176	179
Endocrine & Metabolic Drugs	135	106	11	18	113
Erythropoietin Stimulating Agents	34	12	7	15	107
Estrogen Derivative	11	0	6	5	0
Fibromyalgia	221	36	108	77	316
Fish Oils	24	1	12	11	47
Gastrointestinal Agents	122	34	31	57	134
Genitourinary Agents	16	5	5	6	74
Growth Hormones	99	77	8	14	151
Hematopoietic Agents	19	11	1	7	124
Hepatitis C	159	100	24	35	8
HFA Rescue Inhalers	49	0	18	31	0
Insomnia	28	8	9	11	162
Insulin	125	44	20	61	320
Miscellaneous Antibiotics	19	4	2	13	14
Multiple Sclerosis	67	30	13	24	172
Muscle Relaxant	47	9	15	23	69
Nasal Allergy	73	10	35	28	167
Neurological Agents	84	26	22	36	228
NSAIDs	164	20	44	100	197
Ocular Allergy	33	5	9	19	87
Osteoporosis	34	13	8	13	306
Other*	295	53	79	163	189

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Respiratory Agents	31	18	2	11	138
Statins	14	4	3	7	222
Stimulant	633	301	71	261	346
Testosterone	58	21	13	24	312
Thyroid	10	1	1	8	360
Topical Antifungal	32	9	6	17	23
Topical Corticosteroids	75	1	36	38	358
Vitamin	101	28	40	33	126
Pharmacotherapy	81	63	1	17	306
Emergency PAs	2	2	0	0	
Total	**6,711**	**2,657**	**1,264**	**2,790**	
Overrides					
Brand	23	19	1	3	324
Compound	27	25	0	2	101
Cumulative Early Refill	2	2	0	0	4
Diabetic Supplies	22	11	0	11	151
Dosage Change	300	280	1	19	12
High Dose	4	4	0	0	270
Ingredient Duplication	19	17	0	2	12
Lost/Broken Rx	94	91	0	3	15
NDC vs Age	255	158	24	73	257
Nursing Home Issue	92	74	0	18	15
Opioid Quantity	31	25	4	2	143
Other*	30	27	0	3	21
Quantity vs. Days Supply	571	403	35	133	230
STBS/STBSM	21	13	0	8	79
Stolen	10	9	1	0	15
Temporary Unlock	2	2	0	0	20
Third Brand Request	37	26	3	8	29
Overrides Total	**1,458**	**1,123**	**65**	**270**	
Total Regular PAs + Overrides	**8,169**	**3,780**	**1,329**	**3,060**	

Denial Reasons	
Unable to verify required trials.	2,413
Does not meet established criteria.	1,357
Lack required information to process request.	617
Other PA Activity	
Duplicate Requests	528
Letters	8,986
No Process	6
Changes to existing PAs	706
Helpdesk Initiated Prior Authorizations	613
PAs Missing Information	32

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

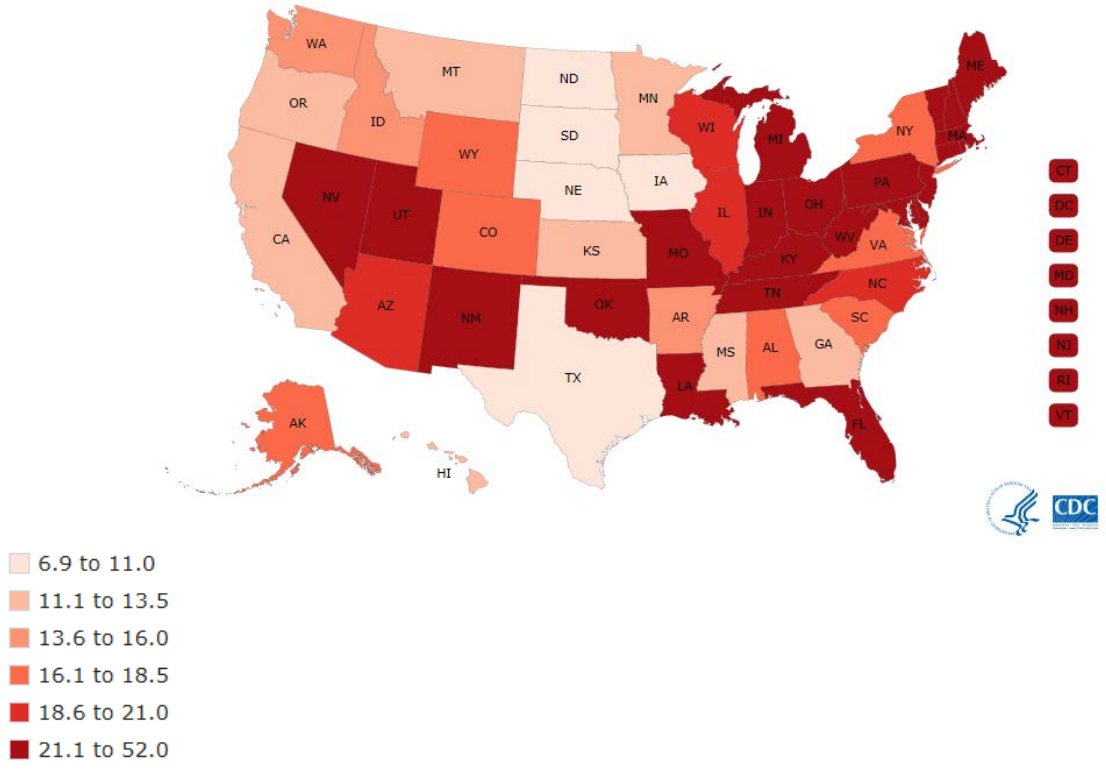
SoonerCare Opioid Initiative Update

Oklahoma Health Care Authority
July 2018
Data and content assistance provided by Burl Beasley, MPH, MS Pharm and Bryon Perdue, Pharmacy Research Analyst

Introduction[1]

In the United States, opioids were involved in 42,249 deaths in 2016, 813 of which were in Oklahoma. Additionally, Oklahoma saw a statistically significant increase in the drug overdose death rate from 2015 to 2016 (13.2% change). The following map from the Centers for Disease Control and Prevention (CDC) highlights the age-adjusted rates of drug overdose deaths by state for 2016. Additional overdose data and SoonerCare opioid prescribing habits can be found in the Oklahoma Health Care Authority's (OHCA) Opioid Education Graphic *(See Attachment A)* at the end of this report.

CDC Number and Age-Adjusted Rates of Drug Overdose Deaths by State (2016)



Morphine Milligram Equivalent (MME) Summary[2,3,4,5,6,7,8,9]

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 following table contains MMEs based on strength and quantities for commonly prescribed opioid medications. MMEs in red font exceed the CDC recommendation of 90 MME per day.

Drug/Strength	Quantity	Day Supply	Daily MME
Immediate-Release (IR) Products			
codeine 30mg	120	30	18
hydrocodone/APAP 5mg/325mg	120	30	20
hydrocodone/APAP 7.5mg/325mg	120	30	30
hydrocodone/APAP 10mg/325mg	120	30	40
hydromorphone IR 2mg	120	30	32
hydromorphone IR 4mg	120	30	64
hydromorphone IR 8mg	120	30	128
oxycodone IR 15mg	120	30	90
oxycodone IR 20mg	120	30	120
oxycodone/APAP 7.5mg/325mg	120	30	45
Extended-Release (ER) Products			
fentanyl patch 25mcg	10	30	60
fentanyl patch 37.5mcg	10	30	90
fentanyl patch 50mcg	10	30	120
fentanyl patch 75mcg	10	30	180
Hysingla® ER (hydrocodone ER) 100mg	30	30	100
Hysingla® ER (hydrocodone ER) 120mg	30	30	120
Oxycontin® (oxycodone ER) 30mg	60	30	90

MME = morphine milligram equivalent; APAP = acetaminophen

The following are MME recommendations or alerts from various government organizations, medical groups, quality measurement programs, and law enforcement:

- CDC: 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.
- Centers for Medicare and Medicaid Services (CMS): In February 2018, CMS proposed that beginning in 2019, initial opioid prescriptions for acute pain be limited to 7 days and no more than 90 MME per day, in addition, CMS suggested that Medicare Part D plans monitor patients taking opioids with "potentiators" such as Neurontin® (gabapentin) and Lyrica® (pregabalin). CMS also proposed a quality measure to track how well Part D plans flag concurrent use of opioids and benzodiazepines.
- Oklahoma Senate Bill (SB) 1446: In May 2018, SB 1446 was signed into law and places a 7-day limit on initial opioid prescriptions. While enforcement and other details of the law are currently pending, many pharmacies and providers are already implementing these limitations.
- Oklahoma Bureau of Narcotics and Dangerous Drugs (OBNDD) Prescription Monitoring Program (PMP): In February 2018, the OBNDD via the AWARE system initiated three clinical alerts featured on the PMP. The clinical alerts were designed to help providers identify at-risk patients. One of the alerts included patients who exceed a daily MME of 100.

- Pharmacy Quality Alliance (PQA) Opioid Measures: PQA, a nationally recognized organization that develops measures to promote appropriate medication use and reporting of performance information related to medications, developed three opioid measures including one specific to opioid analgesics at "high dosages" in persons without cancer. The measure defined "high dosages" as 120 MME or greater.
- Other States: The College of Pharmacy queried other states for their MME limits. The following list details daily MME limits of states who responded to the College of Pharmacy's query:
  - Arkansas: 50 MME for initial prescriptions; 90 MME for chronic prescriptions
  - Florida: 90 MME
  - Indiana: 60 MME for initial prescriptions
  - Kansas: 90 MME
  - Kentucky: 90 MME
  - Maryland: 90 MME
  - Montana: Currently at 180 MME with goal of 90 MME
  - Nevada: 50 MME
  - North Carolina: 90 MME
  - Ohio: 30 MME for initial prescriptions
  - Rhode Island: 30 MME for initial prescriptions
  - Texas: In process of decreasing to 90 MME by January 2019
  - West Virginia: 50 MME
  - Wyoming: 120 MME

SoonerCare MME Claims Analysis

The following table details SoonerCare claims for Schedule II medications for members and prescribers of members exceeding various MME thresholds from January 1, 2018 to March 31, 2018. The table excludes members with an oncology diagnosis in medical claims history over the specified time period evaluated. Combination products containing buprenorphine and naloxone used for medication assisted treatment (MAT), cough and cold products, injections, suppositories, and compounded items were excluded from the analysis.

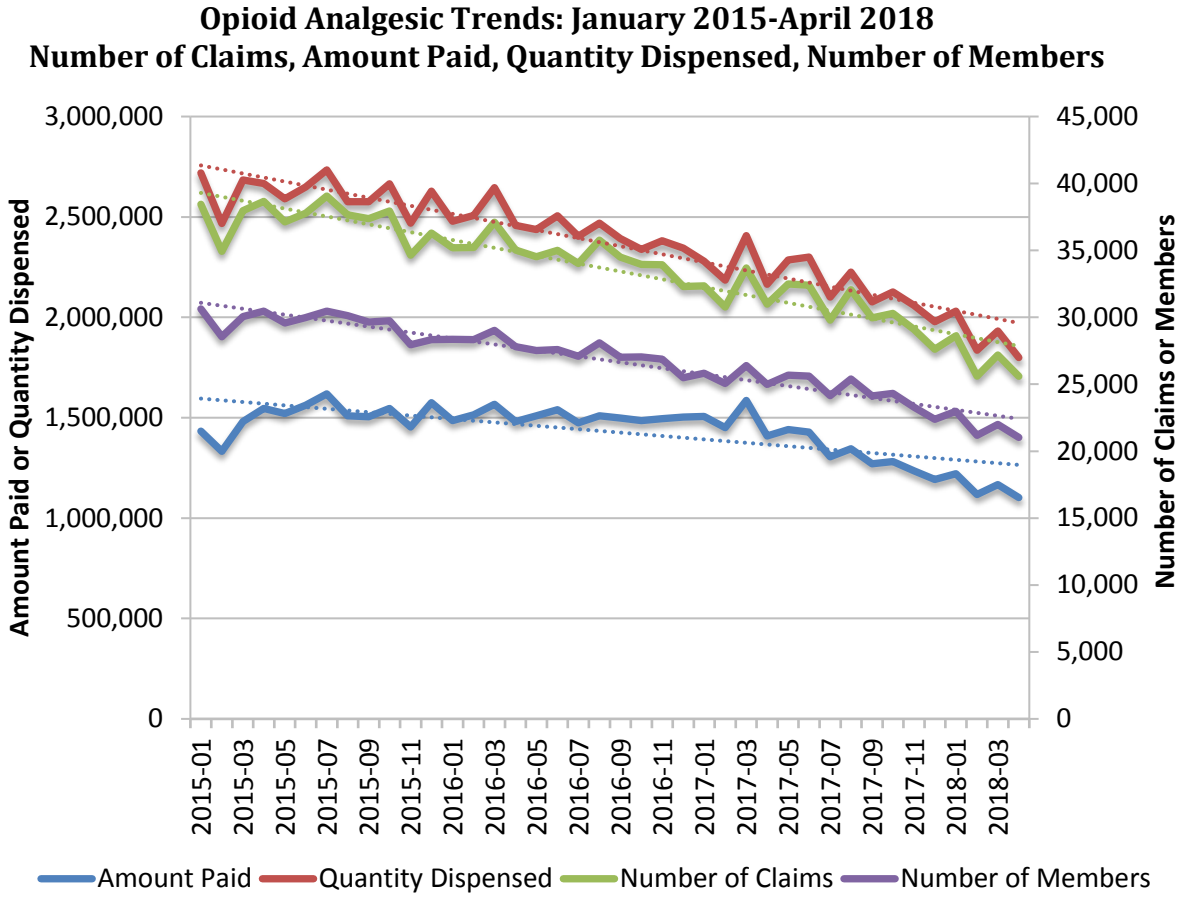
MME Threshold	# of Prescribers	Avg. # of Members Per Prescriber Exceeding MME Threshold	Prescriber Specialties	# of Members	# of Prescriptions
>240 MME	37	1.5	63.2% family or general practitioner; 23.7% internist; all other specialties <10%	57	151
>160 MME	218	2.6	56.6% family or general practitioner; 13.1% internist; all other specialties <10%	573	1,549
>120 MME	240	2.8	58.0% family or general practitioner; 11.9% internist; all other specialties <10%	678	1,842
>100 MME	432	6.5	46.4% family or general practitioner; 11.3% internist; all other specialties <10%	1,417	3,557

MME = morphine milligram equivalent; Avg. = average; # = number

SoonerCare Opioid Claims Analysis[10,11,12,13]

In July 2013, the DUR Board voted to reduce the number of immediate-release (IR) opioid units per claim resulting in a maximum quantity of 120 units per 30-day supply. In November 2014, the College of Pharmacy and the OHCA began implementation of a quantity reduction on all IR, solid dosage form opioid analgesics. The quantity limit was phased in over a 3-month period and was fully implemented by the end of January 2015. In addition to the IR quantity limit, numerous educational efforts have been undertaken by the OHCA and the College of Pharmacy including pain management practice facilitation, naloxone education and access, Lock-In program expansion, as well as newsletter articles and educational mailings. These efforts have coincided with laws passed by the Oklahoma legislature including mandatory PMP checks, which were implemented in November 2015 for prescribers of opioid analgesics to new patients or after 180 days has elapsed since the previous PMP check.

The following chart shows the utilization trends of all 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. (*Of note, hydrocodone became a Schedule II medication on 10/06/2014; mandatory PMP check was implemented 11/01/2015 for prescribers of opioids to new patients or after 180 days elapsed since previous PMP check).*



Additional OHCA Actions

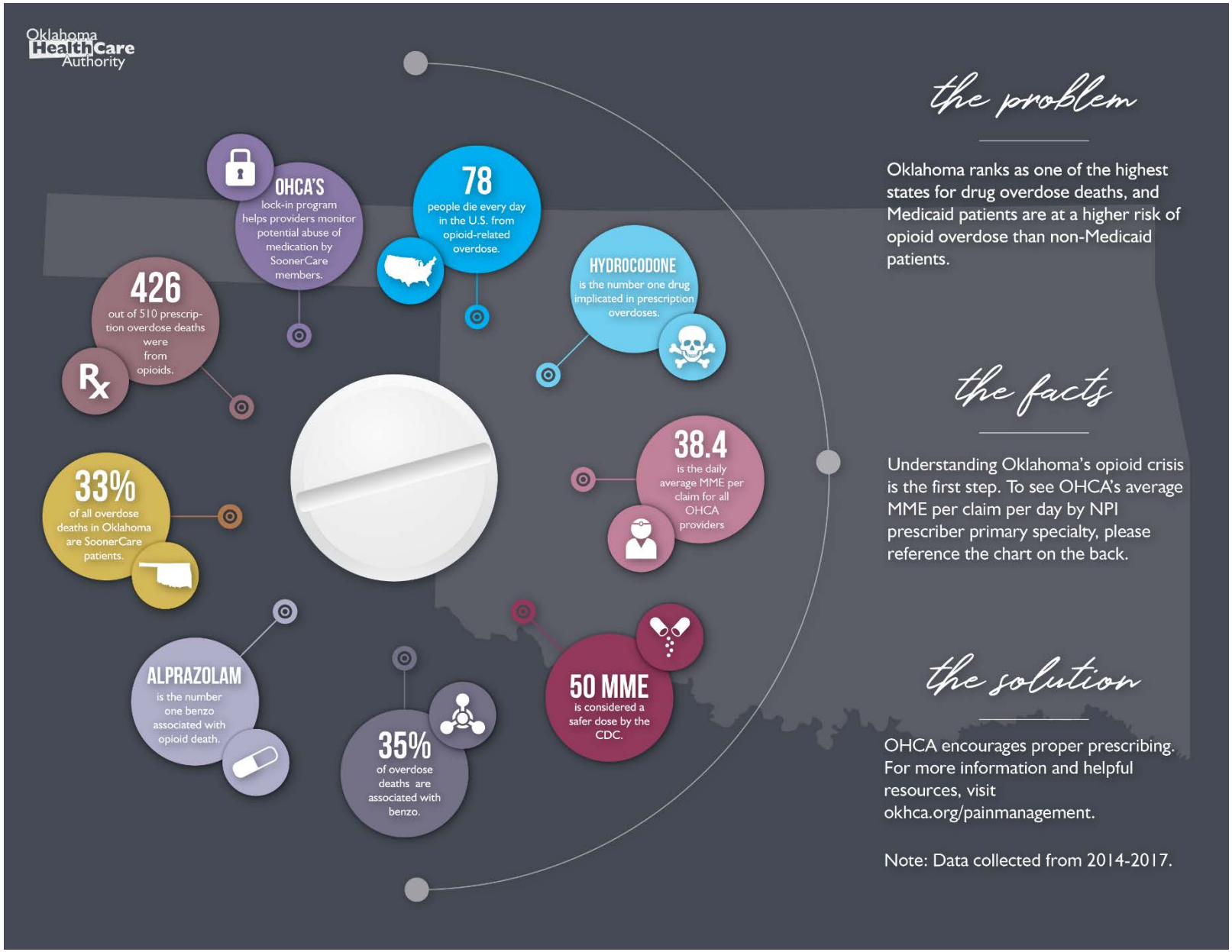
The OHCA is in process of implementing additional early refill edits for non-controlled and controlled medications. Effective November 1, 2018, the threshold for filling a prescription early will increase from 75% of the previous day supply to 80% for non-controlled medications and will increase from 75% of day supply to 85% for controlled medications.

Recommendations

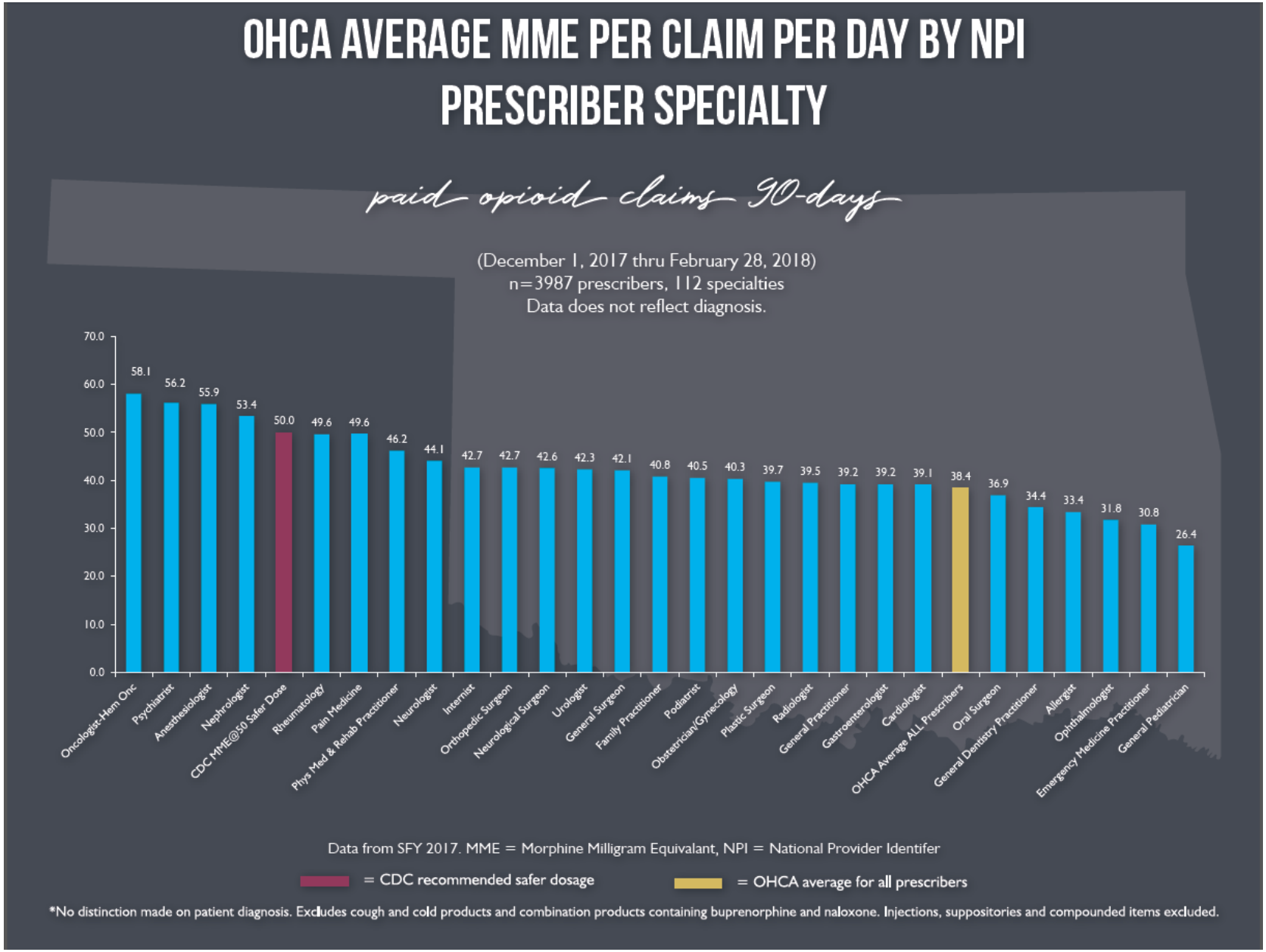
The College of Pharmacy in partnership with the OHCA recommends the implementation of a daily morphine milligram equivalent (MME) limit of 100 to coincide with the Oklahoma Bureau of Narcotics and Dangerous Drugs (OBNDD) clinical alert on the Oklahoma Prescription Monitoring Program (PMP) database.

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

Attachment A: Oklahoma Health Care Authority Opioid Education Graphic[11,12]



Attachment A Continued: Oklahoma Health Care Authority Opioid Education Graphic[11,12]



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Appendix C

Vote to Prior Authorize Crysvita® (Burosumab-twza)

Oklahoma Health Care Authority
July 2018

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

X-linked hypophosphatemia (XLH) is an inherited, X-linked disorder caused by mutations in the *PHEX* gene. Mutations in *PHEX* result in increased concentrations of fibroblast growth factor 23 (FGF23). Excess FGF23 inhibits renal sodium/phosphate cotransporters resulting in inhibition of phosphate reabsorption and causing subsequent hypophosphatemia. Chronic hypophosphatemia leads to poor bone mineralization and fractures. It is estimated that XLH occurs in approximately 1 in 20,000 live births.

XLH is a progressive disorder; however, age of onset, disease severity, and rate of progression vary significantly among affected individuals. Some patients with XLH will only have hypophosphatemia and no bone-related symptoms while others may have more severe symptoms. In most patients, symptoms become apparent in the first 2 years of life when a child begins walking. Initial symptoms include bowing of the legs, short stature, and slowed growth. Additional findings include osteomalacia, bone pain, muscle pain and weakness, waddling gait, joint pain (a result of calcification of tendons and ligaments), abnormal tooth development, tooth abscesses, rickets, fractures, and impaired physical function.

Diagnosis of XLH is based on clinical and laboratory findings. Clinical findings such as slow growth rate, bowing of the legs, or other skeletal abnormalities often prompt initial evaluation. Patients with XLH will have low levels of phosphate, high levels of FGF23, and normal serum calcium and 25-hydroxy vitamin D. Genetic testing can confirm an XLH diagnosis.

Treatment of XLH focuses on reducing discomfort and correcting bone deformation. Children are generally treated from time of diagnosis until closure of growth plates. The mainstay of pediatric treatment is oral phosphate three to five times daily in combination with high-dose calcitriol. Prepubertal children treated with this regimen can show improved radiological signs of rickets, improved growth, correction of deformities in lower limbs, and reduced bone or joint pain. Complications of this regimen may include nephrocalcinosis and hyperparathyroidism. Additional therapies employed include growth hormone and epihysiodesis (growth plate clamping) to mechanically straighten lower extremities during growth. Treatment in adults is less established. Phosphate and calcitriol treatment is generally reserved for adults with skeletal pain, an upcoming orthopedic surgery, evidence of osteomalacia with an elevated alkaline phosphatase, or recurrent pseudofractures or stress fractures. Some patients may also require surgeries to correct bone deformities. Additionally, total hip and knee arthroplasty is sometimes required as a result of degenerative joint disease.

In April 2018, the U.S. Food and Drug Administration (FDA) approved Crysvita® (burosumab-twza), an FGF23 blocking antibody, for the treatment of XLH in adult and pediatric patients 1

year of age and older. Burosumab-twza is the first therapy directed toward correction of renal phosphate wasting, and has efficacy data in repairing skeletal abnormalities including fractures and osteomalacia. Crysvita® (burosumab-twza) is available as single-dose vials intended for subcutaneous (SC) injection in the following strengths: 10mg/mL, 20mg/mL, or 30mg/mL. Burosumab-twza is administered via SC injection and should be administered by a health care provider. Prior to initiation of burosumab-twza, fasting serum phosphorus concentration should be below the reference range for age. Oral phosphate and active vitamin D analogs should be discontinued 1 week prior to initiation of treatment with burosumab-twza. The recommended starting dose in pediatric patients is 0.8mg/kg of body weight, rounded to the nearest 10mg, administered every two weeks. The minimum starting dose is 10mg up to a maximum dose of 90mg. After initiation of treatment, fasting serum phosphorus should be measured every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. The recommended dose in adults is 1mg/kg of body weight, rounded to the nearest 10mg up to a maximum dose of 90mg, administered every four weeks. The wholesale acquisition cost (WAC) of burosumab-twza is $3,400 per 10mg/mL single-dose vial, $6,800 per 20mg/mL single-dose vial, and $10,200 per 30mg/mL single-dose vial.

The College of Pharmacy received input from a geneticist regarding XLH genetic testing. The specialist recommended prior authorization of burosumab-twza to ensure appropriate usage; however, requiring genetic testing as proof of XLH diagnosis was not recommended, but rather it could be used as an option to confirm diagnosis. Laboratory evidence of elevated FGF23 was recommended as an alternative to confirm an XLH diagnosis.

Market News and Updates[8]

News:

- **May 2018:** Ultragenyx Pharmaceutical issued a press release announcing results of a Phase 3 study comparing burosumab-twza to standard therapy (oral phosphate and active vitamin D) in 61 patients 1 to 12 years of age. The study's primary endpoint was the change in rickets at 40 weeks; changes in rickets were evaluated by blinded radiologists using the radiographic global impression of change (RGI-C) scale. Additional secondary endpoints included other rickets assessments using the RGI-C scale and Thacher Rickets Severity Scale (RSS), changes in growth velocity, height, and walking ability. Prior to the study initiation, all enrolled patients had previously received standard therapy for an average of 4 years. A total of 29 patients received burosumab-twza initiated at a dose of 0.8mg/kg every 2 weeks, with dose increases up to 1.2mg/kg occurring in 5 patients. A total of 32 patients received standard therapy based on guideline recommended dosing and physician adjustment.
    - RGI-C Score: After 40 weeks of treatment, the least squares (LS) mean change in RGI-C score was +1.92 for burosumab-twza-treated patients versus +0.77 for standard therapy-treated patients (1.14 treatment difference; P<0.0001).
    - Substantial Healing (Percentage of Patients Achieving RGI-C +2.0): Substantial healing was found in 72% of burosumab-twza-treated patients versus 6% standard therapy-treated patients (odds ratio 39.139; P<0.0001).

- Growth, Height, and Walking Ability: Burosumab-twza did not show statistically significant improvement in growth, height, or 6-minute walk test compared to standard therapy.

Recommendations

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

Crysvita® (Burosumab-twza) Approval Criteria:

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

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

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Appendix D

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

Oklahoma Health Care Authority
July 2018

Introduction[1,2,3,4]

- **Alecensa® (alectinib):** In November 2017, the U.S. Food and Drug Administration (FDA) granted regular approval to Alecensa® (alectinib) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC).
- **Imfinzi® (durvalumab):** In February 2018, the FDA approved Imfinzi® (durvalumab), a programmed death-ligand 1 (PD-L1) blocking antibody, for patients with unresectable stage 3 NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. Durvalumab was previously FDA approved for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- **Keytruda® (pembrolizumab):**
  - In June 2018, the FDA approved Keytruda® (pembrolizumab) for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [combined positive score (CPS) ≥1].
  - In June 2018, the FDA approved Keytruda® (pembrolizumab) for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after two or more prior lines of therapy.
- **Opdivo® (nivolumab):**
  - In December 2017, the FDA granted regular approval to Opdivo® (nivolumab) for adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection. Nivolumab was previously approved for the treatment of patients with unresectable or metastatic melanoma.
  - In March 2018, the FDA approved a supplemental Biologics License Application (sBLA) for updating the Opdivo® (nivolumab) dosing schedule to include 480mg infused every four weeks for a majority of approved indications. The 480mg dose is in addition to the previously approved dosing option of 240mg every two weeks. Nivolumab was also approved for a shorter 30-minute infusion across all approved indications.

- **Opdivo® (nivolumab) and Yervoy® (ipilimumab):** In April 2018, the FDA approved Opdivo® (nivolumab) and Yervoy® (ipilimumab) in combination for the treatment of intermediate or poor risk, previously untreated, advanced renal cell carcinoma (RCC).
- **Tagrisso® (osimertinib):** In April 2018, the FDA approved Tagrisso® (osimertinib) for the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations.

Recommendations

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

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

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

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

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

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

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

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

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

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

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

1. Patient has complete resection of melanoma; and
2. Diagnosis of stage IIIB/C melanoma following complete resection; and
3. The patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
4. Nivolumab must be used as a single-agent; and

5. Dose as follows:
    a. Single-agent: 240mg every two weeks or 480mg every four weeks; and
    b. Maximum duration of one year.

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

1. For nivolumab monotherapy:
    a. A diagnosis of relapsed or surgically unresectable stage IV disease; and
    b. Failed prior therapy with one of the following medications:
        i. Sunitinib; or
        ii. Sorafenib; or
        iii. Pazopanib; or
        iv. Axitinib; or
2. For nivolumab use in combination with ipilimumab:
    a. A diagnosis of relapsed or surgically unresectable stage IV disease in the initial treatment of patients with intermediate or poor risk, previously untreated, advanced RCC; and
3. Patient must have an ECOG performance status of 0 to 2; and
4. The patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
5. Dose as follows:
    a. Single-agent: 240mg every two weeks or 480mg every four weeks; or
    b. In combination with ipilimumab: nivolumab 3mg/kg followed by ipilimumab 1mg/kg on the same day, every three weeks for a maximum of four doses, then nivolumab 240mg every two weeks or 480mg every four weeks.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. Nivolumab must be used as a single-agent, or in combination with ipilimumab:
    a. As first-line therapy for untreated melanoma; or
    b. As second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy:
        i. If the patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
        ii. Patient must have an ECOG performance status of 0 to 2; and
3. Dose as follows:
    a. Single-agent: 240mg every two weeks or 480mg every four weeks; or
    b. In combination with ipilimumab: 1mg/kg, followed by ipilimumab on the same day, every three weeks for four doses, then 240mg every two weeks or 480mg every four weeks.

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

1. Diagnosis of metastatic NSCLC; and
2. Tumor histology is one of the following:
    a. Adenocarcinoma; or
    b. Squamous cell; or

c. Large cell; and
3. Disease progression on or after platinum-containing chemotherapy (e.g., cisplatin, carboplatin); and
4. Patient must have an ECOG performance status of 0 to 2; and
5. The patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
6. Nivolumab must be used as a single-agent; and
7. Dose as follows: 240mg every two weeks or 480mg every four weeks.

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

1. A diagnosis of recurrent or metastatic head and neck cancer; and
2. Squamous cell histology; and
3. Patient has received prior platinum-containing regimen (e.g., cisplatin, carboplatin); and
4. Patient must have an ECOG performance status of 0 to 1; and
5. The patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
6. Dose as follows: ~~3mg/kg every two weeks~~ 240mg every two weeks or 480mg every four weeks.

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

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

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

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

[1] U.S. Food and Drug Administration (FDA). Hematology/Oncology (Cancer) Approvals & Safety Notifications. Available online at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Last revised 06/27/2018. Last accessed 07/02/2018.

[2] Takeda Pharmaceutical Company. Takeda Announces FDA Approval of Alunbrig® (brigatinib) 180mg Tablets. *Business Wire*. Available online at: https://www.businesswire.com/news/home/20171003005791/en/Takeda-Announces-FDA-Approval-ALUNBRIG%C2%AE-brigatinib-180. Issued 10/03/2017. Last accessed 07/02/2018.

[3] Bristol-Myers Squibb Company. Bristol-Myers Squibb's Opdivo® (nivolumab) Now the First and Only FDA-Approved PD-1 Inhibitor to Offer Every Four-Week Dosing. *Business Wire*. Available online at: https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibbs-opdivo-nivolumab-now-first-and-only-fda-. Issued 03/06/2018. Last accessed 07/02/2018.

[4] Imfinzi® Prescribing Information. AstraZeneca. Available online at: https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1. Last revised 02/2018. Last accessed 07/02/2018.

Appendix E

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

Oklahoma Health Care Authority
July 2018

Introduction[1,2,3,4]

- **Erleada™ (apalutamide):** In February 2018, the U.S. Food and Drug Administration (FDA) approved Erleada™ (apalutamide), an androgen receptor inhibitor, for the treatment of patients with non-metastatic, castration-resistant prostate cancer (CRPC). Erleada™ is supplied as 60mg oral tablets. The recommended dose is 240mg (four 60mg tablets) by mouth once daily. Patients should also receive a concomitant gonadotropin-releasing hormone (GnRH) analog or should have had bilateral orchiectomy. The wholesale acquisition cost (WAC) per Erleada™ 60mg tablet is $91.00, resulting in a daily cost of $364.00.
- **Zytiga® (abiraterone):** In February 2018, the FDA approved Zytiga® (abiraterone), a CYP17 inhibitor, for use in combination with prednisone for the treatment of metastatic, high-risk, castration-sensitive prostate cancer (CSPC). Zytiga® was previously approved for use in metastatic, CRPC. Zytiga® is supplied as 250mg and 500mg oral tablets. The recommended dose is 1,000mg by mouth once daily. Patients should also receive a concomitant GnRH analog or should have had bilateral orchiectomy. Zytiga® should be administered with prednisone 5mg twice daily in CRPC or prednisone 5mg once daily in CSPC. The WAC per Zytiga® 500mg tablet is $170.54, resulting in a daily cost of $341.08.
- **Yonsa® (abiraterone):** In May 2018, the FDA approved Yonsa® (abiraterone), an ultramicrosize formulation of the oral CYP17 inhibitor abiraterone acetate (approved as Zytiga®), to be used in combination with methylprednisolone for the treatment of metastatic, CRPC. Yonsa® is supplied as 125mg oral tablets. The recommended dosing is 500mg (four 125mg tablets) by mouth once daily. Patients should also receive a concomitant GnRH analog or should have had bilateral orchiectomy and Yonsa® should be administered with methylprednisolone 4mg by mouth twice daily. The WAC per Yonsa® 125mg tablet is $76.74, resulting in a daily cost of $306.96.

Recommendations

Erleada™ (Apalutamide) Approval Criteria:

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

Yonsa® (Abiraterone) Approval Criteria:

1. A diagnosis of metastatic, castration-resistant prostate cancer (CRPC); and

2. Concomitant treatment with a gonadotropin-releasing hormone (GnRH) analog or prior history of bilateral orchiectomy.
3. Abiraterone must be used in combination with a corticosteroid.

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

1. A diagnosis of metastatic, high-risk, CSPC; and
2. Member must have high-risk disease defined as having at least two of the following risk factors:
    a. Total Gleason score of ≥8; or
    b. Presence of ≥3 lesions on bone scan; or
    c. Evidence of measurable visceral metastases; and
3. Abiraterone must be used in combination with a corticosteroid.

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[1] U.S. Food and Drug Administration (FDA). Hematology/Oncology (Cancer) Approvals & Safety Notifications. Available online at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Last revised 06/27/2018. Last accessed 07/02/2018.

[2] FDA. FDA approves apalutamide for non-metastatic castration-resistant prostate cancer. Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm596796.htm. Issued 02/14/2018. Last accessed 07/02/2018.

[3] Erleada™ Prescribing Information. Janssen Pharmaceutical Companies. Available online at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf. Last revised 02/2018. Last accessed 07/02/2018.

[4] Yonsa® Prescribing Information. Sun Pharmaceutical Industries, Inc. Available online at: http://dobuu0g5h7yu1.cloudfront.net/wp-content/uploads/sites/3/2018/05/Yonsa-PI.pdf. Last revised 05/2018. Last accessed 07/02/2018.

Appendix F

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

Oklahoma Health Care Authority
July 2018

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

- **Cotempla XR-ODT™ [methylphenidate extended-release (ER) orally disintegrating tablet (ODT)]** was approved by the U.S. Food and Drug Administration (FDA) in June 2017 for the treatment of ADHD in patients 6 to 17 years of age. Cotempla XR-ODT™ is available as grape-flavored methylphenidate ER ODTs in the following strengths: 8.6mg, 17.3mg, and 25.9mg, which is the same amount of methylphenidate (base equivalent) found, respectively, in 10mg, 20mg, and 30mg strength methylphenidate hydrochloride products. Cotempla XR-ODT™ contains approximately 25% immediate-release (IR) and 75% ER methylphenidate. Cotempla XR-ODT™ should be administered orally once daily in the morning with or without food; the maximum recommended dose of Cotempla XR-ODT™ is 51.8mg once daily. The national average drug acquisition cost (NADAC) of Cotempla XR-ODT™ 25.9mg is $10.34 per ODT, which results in a monthly cost of $620.40, based on the maximum dose of 51.8mg per day (two 25.9mg ODTs per day).
- **Mydayis® (amphetamine/dextroamphetamine ER capsule)** was FDA approved in June 2017 for the treatment of ADHD in patients 13 years of age and older. Mydayis® is not for use in children 12 years of age and younger. Pediatric patients 12 years of age and younger experienced higher plasma exposure than patients 13 years of age and older at the same dose of Mydayis® and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite. Mydayis® is available as amphetamine/ dextroamphetamine ER capsules in the following strengths: 12.5mg, 25mg, 37.5mg, and 50mg. Mydayis® capsules contain equal amounts of three types of drug-releasing beads, an IR and two different types of delayed-release (DR) beads. Mydayis® should be administered once daily in the morning upon awakening with or without food; the maximum recommended dose of Mydayis® is 25mg once daily (pediatric patients 13 to 17 years of age) or 50mg once daily (adult patients 18 to 55 years of age). The NADAC of Mydayis® ranges from $8.54 to $8.66 per capsule, depending on strength, which results in a monthly cost of $256.20 to $259.80, based on the recommended dosing of one capsule per day.
- **Adzenys ER™ (amphetamine ER suspension)** was FDA approved in September 2017 for the treatment of ADHD in patients 6 years of age and older. Adzenys ER™ is available as an orange-flavored amphetamine 1.25mg/mL ER oral suspension. Adzenys ER™ suspension does not require refrigeration, does not require reconstitution at the pharmacy level, and is available in a 450mL bottle. Adzenys ER™ contains approximately

equal amounts of IR and DR amphetamine. Adzenys ER™ should be administered orally once daily in the morning with or without food; the maximum recommended dose of Adzenys ER™ is 18.8mg (15mL) once daily (patients 6 to 12 years of age) or 12.5mg (10mL) once daily (patients 13 years of age and older). The wholesale acquisition cost (WAC) of Adzenys ER™ is $1.42 per milliliter, which results in a monthly cost of $639.00, based on the maximum dose of 18.8mg per day (15mL per day) for patients 6 to 12 years of age, or $426.00 per month, based on the maximum dose of 12.5mg per day (10mL per day) for patients 13 years of age and older.

Recommendations

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

ADHD Medications Tier-2 Approval Criteria:

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

ADHD Medications Tier-3 Approval Criteria:

1. A covered diagnosis; and
2. A previously failed trial with at least one long-acting Tier-1 stimulant that resulted in an inadequate response; and
3. A previously failed trial with at least one long-acting Tier-2 stimulant that resulted in an inadequate response:
    a. Trials should have been within the last 365 days; and
    b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
    c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.

4. A clinical exception may apply for special formulation products when there is a patient-specific, clinically significant reason why the member cannot use the available long-acting lower tiered formulations.
5. Use of Kapvay® (clonidine extended-release tablets) requires:
    a. An FDA approved diagnosis; and
    b. Previously failed trials (within the last 180 days) with a long-acting Tier-1 stimulant, a long-acting Tier-2 stimulant, Intuniv®, and Strattera®, unless contraindicated, that did not yield adequate results; and
    c. A patient-specific, clinically significant reason why the member cannot use clonidine immediate-release tablets.

ADHD Medications Special Prior Authorization (PA) Approval Criteria:

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

ADHD Medications Additional Criteria:

1. Doses exceeding 1.5 times the FDA maximum are not covered.
2. Prior authorization is required for all tiers for members older than 20 years of age and for members younger than 5 years of age. All prior authorization requests for members younger than 5 years of age must be reviewed by an Oklahoma Health Care Authority (OHCA)-contracted psychiatrist.
3. Vyvanse® (Lisdexamfetamine) Approval Criteria [Binge Eating Disorder (BED) Diagnosis]:
    a. An FDA approved diagnosis of moderate-to-severe binge eating disorder (BED); and
    b. Member must be 18 years of age or older; and
    c. Vyvanse® for the diagnosis of BED must be prescribed by a psychiatrist; and

d. Authorizations will not be granted for the purpose of weight loss without the diagnosis of BED or for the diagnosis of obesity alone. The safety and effectiveness of Vyvanse® for the treatment of obesity have not been established; and
e. A quantity limit of 30 capsules or chewable tablets per 30 days will apply; and
f. Initial approvals will be for the duration of three months. Continued authorization will require prescriber documentation of improved response/effectiveness of Vyvanse®.

Narcolepsy Medications Approval Criteria:

1. An FDA approved diagnosis; and
2. Use of 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 brand name preferred 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			Adzenys ER™ (amphetamine ER susp) Adzenys XR-ODT® (amphetamine ER-ODT) Cotempla XR-ODT™ (methylphenidate ER ODT) Daytrana® (methylphenidate ER) Desoxyn® (methamphetamine) Dexedrine® (dextroamphetamine) Dexedrine Spansules® (dextroamphetamine ER) Dyanavel® XR (amphetamine ER susp) Evekeo® (amphetamine) Methylin® (methylphenidate soln & chew tabs) Mydayis® (amphetamine/ dextroamphetamine ER) ProCentra® (dextroamphetamine) Zenzedi® (dextroamphetamine)
Short-Acting			
Adderall® (amphetamine/ dextroamphetamine)			
Long-Acting			
Vyvanse® (lisdexamfetamine caps and chew tabs)+	Adderall XR® brand name only (amphetamine/ dextroamphetamine ER)	amphetamine/ dextroamphetamine ER (generic Adderall XR®)	
Methylphenidate			
Short-Acting			
Focalin® (dexmethylphenidate) Methylin® (methylphenidate) Ritalin® (methylphenidate)			
Long-Acting			
Aptensio XR® (methylphenidate ER) Focalin XR® brand name only (dexmethylphenidate ER) Metadate CD® (methylphenidate ER) QuilliChew ER® (methylphenidate ER chew tabs) Ritalin LA® (methylphenidate ER)	dexmethylphenidate ER (generic Focalin XR®) Quillivant XR® (methylphenidate ER susp)	Concerta® (methylphenidate ER) Metadate ER® (methylphenidate ER) Methylin ER® (methylphenidate ER) Ritalin SR® (methylphenidate ER)	
Non-Stimulants			
Intuniv® (guanfacine ER) Strattera® (atomoxetine)		Kapvay® (clonidine ER)Δ	

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

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

ΔUnique criteria applies in addition to tier trial requirements.

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

[1] Neos Therapeutics, Inc. Neos Therapeutics Announces FDA Approval of Cotempla XR-ODT™ (Methylphenidate) Extended-Release Orally Disintegrating Tablets for the Treatment of ADHD in Patients 6 to 17 Years Old. *Globe Newswire.* Available online at: https://globenewswire.com/news-release/2017/06/20/1026029/0/en/Neos-Therapeutics-Announces-FDA-Approval-of-Cotempla-XR-ODT-methylphenidate-Extended-Release-Orally-Disintegrating-Tablets-for-the-Treatment-of-ADHD-in-Patients-6-to-17-Years-Old.html. Issued 06/19/2017. Last accessed 06/15/2018.

[2] Cotempla XR-ODT™ (Methylphenidate ER ODT) Prescribing Information. Neos Therapeutics, Inc. Available online at: http://www.neostxcontent.com/Labeling/Cotempla/Cotempla_PI.pdf. Last revised 06/2017. Last accessed 06/15/2018.

[3] Cotempla XR-ODT™ (Methylphenidate ER ODT) Package Insert. Medlibrary.org. Available online at: https://medlibrary.org/lib/rx/meds/cotempla-xr-odt/. Last revised 06/28/2017. Last accessed 06/15/2018.

[4] Shire. Shire plc: U.S. FDA Approves Mydayis® (Mixed Salts of a Single-Entity Amphetamine Product) – A New Once-Daily Option for ADHD Symptom Control in Patients 13 Years and Older. *PR Newswire.* Available online at: https://www.prnewswire.com/news-releases/shire-plc-us-fda-approves-mydayistm-mixed-salts-of-a-single-entity-amphetamine-product---a-new-once-daily-option-for-adhd-symptom-control-in-patients-13-years-and-older-629760653.html. Issued 06/20/2017. Last accessed 06/15/2018.

[5] Mydayis® (Amphetamine/Dextroamphetamine ER Capsules) Prescribing Information. Shire U.S., Inc. Available online at: http://pi.shirecontent.com/?product=MYD&country=USA&language=ENG. Last revised 06/2017. Last accessed 06/15/2018.

[6] Mydayis® (Amphetamine/Dextroamphetamine ER Capsules) Package Insert. Medlibrary.org. Available online at: https://medlibrary.org/lib/rx/meds/mydayis/. Last revised 06/28/2017. Last accessed 06/15/2018.

[7] Neos Therapeutics, Inc. Neos Therapeutics Receives U.S. FDA Approval of Adzenys ER™ (Amphetamine) Extended-Release Oral Suspension for the Treatment of ADHD in Patients 6 Years and Older. *Globe Newswire.* Available online at: https://globenewswire.com/news-release/2017/09/15/1123438/0/en/Neos-Therapeutics-Receives-U-S-FDA-Approval-of-Adzenys-ER-amphetamine-Extended-Release-Oral-Suspension-for-the-Treatment-of-ADHD-in-Patients-6-Years-and-Older.html. Issued 09/15/2017. Last accessed 06/15/2018.

[8] Adzenys ER™ (Amphetamine ER Suspension) Prescribing Information. Neos Therapeutics, Inc. Available online at: http://www.neostxcontent.com/Labeling/AdzenysER/AdzenysER_PI.pdf. Last revised 09/2017. Last accessed 06/15/2018.

[9] Adzenys ER™ (Amphetamine ER Suspension) Package Insert. Medlibrary.org. Available online at: https://medlibrary.org/lib/rx/meds/adzenys-er-1/. Last revised 12/08/2017. Last accessed 06/15/2018.

Appendix G

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

Oklahoma Health Care Authority
July 2018

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

Baclofen 5mg tablet is a muscle relaxant indicated for muscle spasticity. The determination of optimal dosage requires individual titration. It is recommended to start therapy at a low dosage (5mg three times daily) and increase gradually until optimum effect is achieved (usually between 40 to 80mg daily). The total daily dose should not exceed 80mg.

- Other Formulation(s) Available: baclofen 10mg tablets

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days*
baclofen 5mg tablets	**$0.93**	**$223.20**
baclofen 10mg tablets	$0.10	$12.00

Unit = tablet
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 30 days based on usual effective dosing of 40mg daily.

Esomep-EZS™ (esomeprazole kit) is a proton pump inhibitor indicated for treatment of gastroesophageal reflux disease (GERD), risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer(s), *Helicobacter pylori (H. pylori)* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions, including Zollinger-Ellison syndrome. It is supplied in a kit containing a quantity of 30 esomeprazole magnesium 20mg delayed-release (DR) capsules along with 59mL of PharmapureRx® Pill Swallowing Spray™. The recommended dose of esomeprazole varies according to diagnosis. It is recommended to use one to two sprays of PharmapureRx® Pill Swallowing Spray™ to coat the tongue and throat, then place the capsule on the tongue and swallow immediately with water.

- Other Formulation(s) Available: esomeprazole DR capsules, Nexium® oral suspension granules, and omeprazole DR capsules

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days
Esomep-EZS™ (esomeprazole kit)	**$358.30**	**$358.30**
esomeprazole DR capsules 20mg	$0.56	$16.80
Nexium® (esomeprazole) oral suspension granules 20mg	$8.67	$260.10
omeprazole DR capsules 20mg	$0.04	$1.20

Unit = capsule, kit, or granule packet; DR = delayed-release
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.

Lyrica® CR [pregabalin extended-release (ER)] is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). The efficacy of Lyrica® CR has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial-onset seizures. It is supplied as an oral tablet in three strengths: 82.5mg, 165mg, and 330mg. The recommended starting dose for DPN and PHN pain is 165mg daily.

- Other Formulation(s) Available: Lyrica® capsules, gabapentin capsules, and gabapentin tablets

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days*
Lyrica® CR (pregabalin ER) tablets 165mg	**$12.77**	**$383.10**
Lyrica® (pregabalin) capsules 150mg	$7.14	$428.40
gabapentin 300mg capsules	$0.04	$3.60

Unit = tablet or capsule; ER = extended-release
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 30 days based on recommended dose for PHN.

Restasis MultiDose® (cyclosporine 0.05% ophthalmic emulsion) is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Restasis MultiDose® is supplied as cyclosporine 0.05% ophthalmic emulsion packaged in a sterile, multi-dose, preservative-free 10mL bottle containing 5.5mL of emulsion. Each bottle contains a unidirectional valve and air filter. Restasis MultiDose® should be administered as one drop in each eye twice daily, approximately 12 hours apart.

- Other Formulation(s) Available: Restasis® (cyclosporine 0.05% single-use vials)

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days
Restasis MultiDose® (cyclosporine 0.05% multi-dose bottle)	**$88.12**	**$484.60**
Restasis® (cyclosporine 0.05% single-use vial)	$8.15	$489.00

Unit = single-use vial or mL
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.

Sinuva™ (mometasone furoate sinus implant) is a corticosteroid-eluting implant indicated for the treatment of nasal polyps in adults 18 years of age and older who have had ethmoid sinus surgery. It contains 1,350mcg of mometasone furoate in a sterile, disposable delivery system. Sinuva™ is loaded into a delivery system and placed in the ethmoid sinus under endoscopic visualization by a physician trained in otolaryngology. The implant may be left in the sinus to gradually release the corticosteroid over 90 days. Repeat administration of Sinuva™ has not been studied.

- Other Formulation(s) Available: mometasone furoate nasal spray

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 90 Days
Sinuva™ (mometasone furoate sinus implant) 1,350mcg	**$1,275.00**	**$2,550.00***
mometasone furoate nasal spray 50mcg	$3.74	$381.48[+]

Unit = implant or gram
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 90 days includes bilateral implants and based on usual treatment duration of Sinuva™.
[+]Cost per 90 days for mometasone furoate nasal spray based on recommended dosing for nasal polyps.

Specialist Recommendation(s): The College of Pharmacy received input from an otolaryngology specialist regarding corticosteroid trials. The specialist recommended prior authorization of Sinuva™ to ensure appropriate usage, and recommended a minimum of a three-month trial of intranasal corticosteroids. The specialist also recommended a trial of systemic corticosteroids, if not medically contraindicated, and that the member have recurrent or chronic sinusitis and recurrent nasal obstruction due to nasal polyps.

Xepi™ (ozenoxacin 1% cream) is a quinolone antimicrobial indicated for the topical treatment of impetigo due to *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* (*S. pyogenes*) in adult and pediatric patients 2 months of age and older. It is supplied in 10g, 30g, and 45g tubes. Each gram of cream contains 10mg of ozenoxacin. Xepi™ is to be applied topically in a thin layer to the affected area(s) twice daily for 5 days.

- Other Formulation(s) Available: gentamicin 0.1% cream and mupirocin 2% ointment

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per Treatment
Xepi™ (ozenoxacin 1% cream)	**Unknown**	**Unknown**
gentamicin 0.1% cream	$2.18	$65.40
mupirocin 2% ointment	$0.22	$4.84

Unit = gram
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.

Xhance™ (fluticasone propionate nasal spray) is a corticosteroid indicated for the treatment of nasal polyps in patients 18 years of age or older. It is supplied in an amber glass bottle fitted with a metered-dose manual spray pump unit inside the device with a nasal applicator, valve mechanism, asymmetrical cone-shaped nosepiece, flexible mouthpiece, and cap. Xhance™ is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the device. The recommended dose is one spray per nostril

twice daily (total daily dose of 372mcg). A dose of two sprays per nostril twice daily may also be effective in some patients (total daily dose of 744mcg).

- Other Formulation(s) Available: fluticasone propionate nasal spray and mometasone furoate nasal spray

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days*
Xhance™ (fluticasone propionate nasal spray) 93mcg	**$26.56**	**$424.96**
fluticasone propionate nasal spray 50mcg	$0.24	$7.68
mometasone furoate nasal spray 50mcg	$3.74	$127.16

Unit = gram or mL
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 30 days based on dosing for nasal polyps.

ZTlido™ (lidocaine 1.8% topical system) contains lidocaine, an amide local anesthetic, and is indicated for relief of pain associated with PHN. It is supplied as a carton of 30 single-use topical systems in individual child-resistant envelopes. ZTlido™ is recommended to be applied to intact skin to cover the most painful area. The prescribed number of topical systems (maximum of three per day) should be applied once for up to 12 hours within a 24-hour period (12 hours on and 12 hours off).

- Other Formulation(s) Available: lidocaine 5% topical patch

Formulation Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days
ZTlido™ (lidocaine 1.8% topical system)	**Unknown**	**Unknown**
lidocaine 5% topical patch	$2.74	$82.20

Unit = topical system or patch
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.

Specialist Recommendation(s): The National Institute for Health and Care Excellence (NICE) recommends the use of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia). The use of topical treatment is recommended for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Recommendations

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

Baclofen 5mg Tablet Approval Criteria:

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

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

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

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

Esomep-EZS™ (Esomeprazole Kit) Approval Criteria:

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

Anti-Ulcer Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA***
omeprazole (Prilosec® caps)	dexlansoprazole (Dexilant® caps)	esomeprazole (Nexium® caps, I.V.)	cimetidine tabs (Tagamet®)
pantoprazole (Protonix® tabs)	esomeprazole (Nexium® packets)	esomeprazole strontium caps	**esomeprazole kit (Esomep-EZS™)**
	lansoprazole (Prevacid® caps, ODT)	dexlansoprazole (Dexilant® SoluTab)	famotidine (Pepcid® susp)
	pantoprazole (Protonix® I.V.)	omeprazole (Prilosec® susp, powder)	nizatidine caps & sol (Axid®)
	rabeprazole sodium (Aciphex® tabs)	pantoprazole (Protonix® susp)	omeprazole/sodium bicarbonate (Zegerid®)
		rabeprazole sodium (Aciphex® Sprinkles)	ranitidine caps
			sucralfate susp unit dose cups

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

Additionally, the College of Pharmacy recommends the prior authorization of Lyrica® CR [pregabalin extended-release (ER)], Restasis MultiDose® (cyclosporine 0.05% ophthalmic

emulsion), Sinuva™ (mometasone furoate sinus implant), and ZTlido™ (lidocaine 1.8% topical system) with the following criteria:

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

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

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

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

Sinuva™ (Mometasone Furoate Sinus Implant) Approval Criteria:

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

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

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

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

Xhance™ (Fluticasone Propionate Nasal Spray) Approval Criteria:

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

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

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

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

Topical Antibiotic Tier-2 Approval Criteria:

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

Topical Antibiotics	
Tier-1	**Tier-2**
gentamicin cream 0.1% (Garamycin®)	mupirocin cream 2% (Bactroban®)
gentamicin ointment 0.1% (Garamycin®)	mupirocin kit 2% (Centany®)
gentamicin powder	mupirocin nasal ointment 2% (Bactroban®)
neomycin/polymixin B sulfates/ bacitracin zinc/hydrocortisone ointment 1% (Cortisporin®)	**ozenoxacin 1% cream (Xepi™)**
neomycin/polymixin B sulfates/hydrocortisone cream 0.5% (Cortisporin®)	retapamulin ointment 1% (Altabax®)
mupirocin ointment 2% (Bactroban®)	

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

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[3] Lyrica® CR Prescribing Information. Pfizer, Inc. Available online at: http://labeling.pfizer.com/ShowLabeling.aspx?id=9678. Last revised 10/2017. Last accessed 06/12/2018.

[4] Restasis MultiDose® Prescribing Information. Allergan. Available online at: https://www.allergan.com/assets/pdf/restasis-combined_pi.pdf. Last revised 10/2016. Last accessed 06/12/2018.

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[8] ZTlido™ Prescribing Information. Scilex Pharmaceuticals, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207962s000lbl.pdf. Last revised 02/2018. Last accessed 06/12/2018.

[9] Neuropathic pain in adults: pharmacological management in non-specialist settings. National Institute for Health and Care Excellence (NICE). NICE Guidance. Available online at: https://www.nice.org.uk/guidance/CG173. Issued 11/2013. Last accessed 06/12/2018.

Appendix H

Calendar Year 2017 Annual Review of Atopic Dermatitis (AD) Medications

Oklahoma Health Care Authority
July 2018

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; and
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; and
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); and
4. Quantities will be limited to 30 grams for use on the face, neck, and groin, and 100 grams for all other areas; and
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 topical corticosteroids; or
2. Atopic dermatitis of face or groin where prescriber does not want to use topical corticosteroids; or
3. Prescribed by a dermatologist.

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

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 be an advanced care practitioner with a supervising physician who is a dermatologist, allergist, or immunologist); and
5. Requests for concurrent use of Dupixent® with other biologic medications will be reviewed on a case-by-case basis and will require patient-specific information to support the concurrent use. (Dupixent® has not been studied in combination with other biologic therapies.)
6. 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.

Eucrisa® (Crisaborole Ointment) Approval Criteria:

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

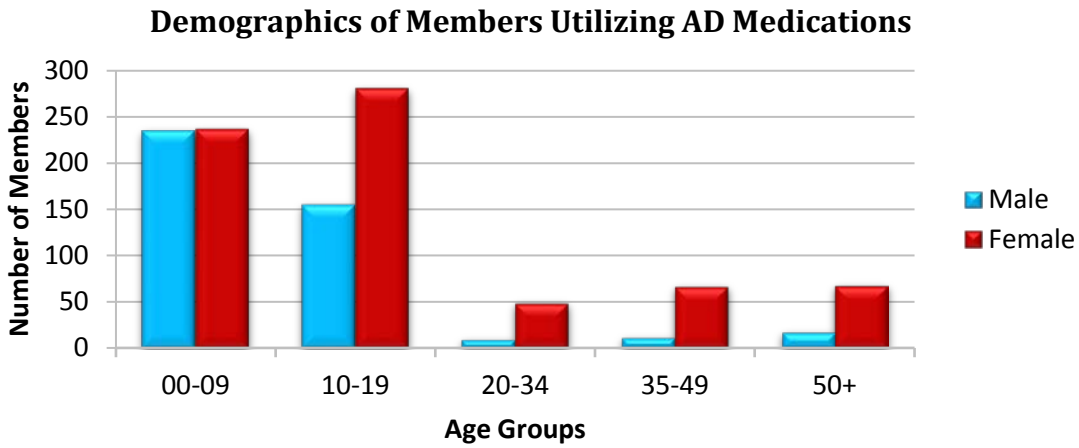
Utilization of AD Medications: Calendar Year 2017

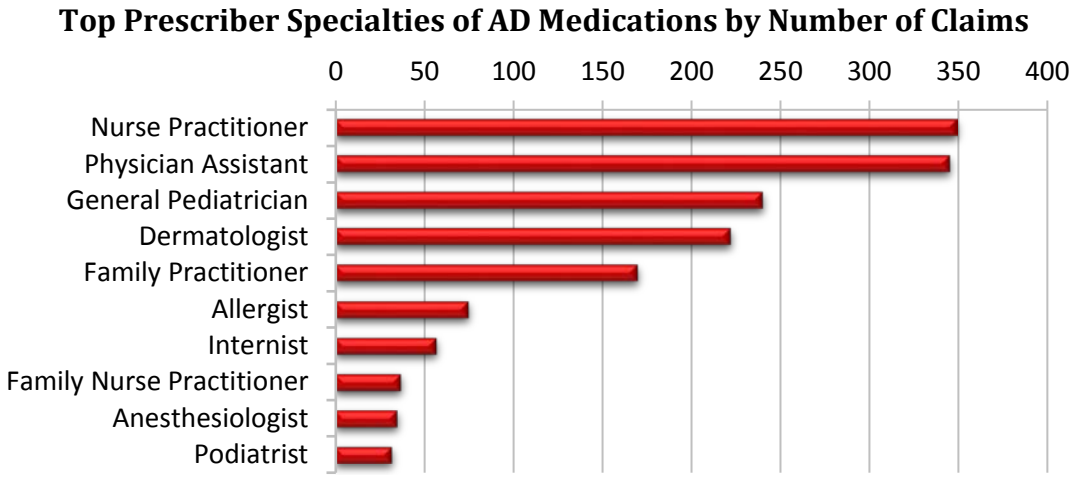
Comparison of Calendar Years

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	1,118	1,620	$512,562.38	$316.40	$9.97	80,090	51,415
2017	1,129	1,620	$689,046.44	$425.34	$13.58	90,386	50,749
% Change	**1.00%**	**0.00%**	**34.40%**	**34.40%**	**36.20%**	**12.90%**	**-1.30%**
Change	**11**	**0**	**$176,484.06**	**$108.94**	**$3.61**	**10,296**	**-666**

*Total number of unduplicated members.

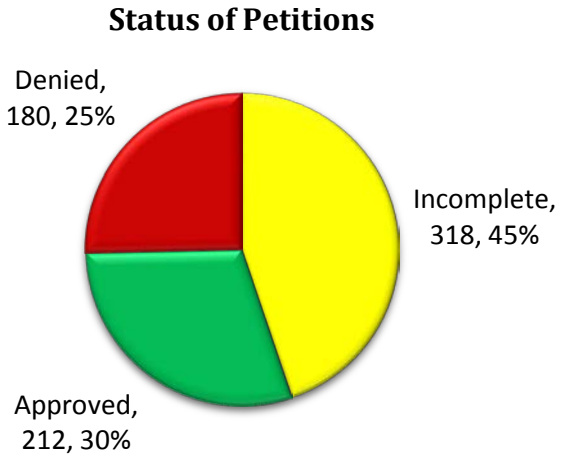
Costs do not reflect rebated prices or net costs.





Prior Authorization of AD Medications

There were 710 prior authorization requests submitted for AD medications during calendar year 2017. 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]

Anticipated Patent Expiration(s):

- Elidel® (pimecrolimus): December 2018
- Eucrisa® (crisaborole): January 2030

Pipeline:

- **Dupilumab:** In May 2018, results from a Phase 3 trial evaluating Dupixent® (dupilumab) for the treatment of moderate-to-severe atopic dermatitis (AD) in adolescents (12 to 17 years of age) were released. Treatment with dupilumab as monotherapy significantly improved measures of overall disease severity, skin clearing, itching, and certain health-related quality of life measures. The primary endpoints were the proportion of patients achieving Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost-clear) and 75% improvement in Eczema Area and Severity Index (EASI-75) at 16 weeks. In the trial, 24% of patients who received weight-based dosing of dupilumab every two weeks (200mg or 300mg) and 18% of patients who received a fixed dose of dupilumab every four weeks (300mg) achieved the primary endpoint – clear or almost-clear skin (IGA; score of 0 or 1) – compared to 2% with placebo ($P<0.0001$ and $P=0.0007$, respectively). For the 16-week treatment period, the overall rate of adverse events was comparable between the dupilumab groups and placebo. There were no serious adverse events or events leading to treatment discontinuation. United States regulatory submission of this data is planned for the third quarter of 2018. In 2016, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for dupilumab for the treatment of moderate-to-severe (12 to 17 years of age) and severe (6 months to 11 years of age) AD. Sanofi and Regeneron are studying dupilumab in a broad range of clinical development programs, including asthma (Phase 3), pediatric AD (Phase 3, ages 6 months to 11 years), nasal polyps (Phase 3), and eosinophilic esophagitis (Phase 2). Future trials are also planned for chronic obstructive pulmonary disease, grass allergy, and food allergy (including peanut).
- **Tralokinumab:** Leo Pharma announced in February 2018 that it had started enrollment for a third Phase 3 clinical study of tralokinumab, an investigational, fully human monoclonal antibody that blocks the effects of cytokine interleukin (IL)-13 for the treatment of moderate-to-severe AD. ECZTRA 3 (ECZema TRAlokinumab trial no. 3) is a randomized, double-blind, placebo-controlled, Phase 3 trial to evaluate the safety and efficacy of tralokinumab in combination with topical corticosteroids (TCS) in patients with moderate-to-severe AD who are candidates for systemic therapy. In March 2017, Leo Pharma announced positive results from a Phase 2b dose-ranging efficacy and safety study of tralokinumab in adult patients with moderate-to-severe AD. The double-blind study included 204 patients who had moderate-to-severe AD despite a two-week run-in with continuous mid-strength TCS treatment. Patients were randomized to receive tralokinumab (45, 150, or 300mg) or placebo by subcutaneous administration every two weeks for 12 weeks. After treatment with tralokinumab for 12 weeks, 150mg and 300mg tralokinumab 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. The number of patients achieving a 50% improvement from baseline in the EASI (EASI-50) at

week 12 in the tralokinumab 300mg group was significantly higher compared with placebo (73.4% vs. 51.9%, P=0.025).

- **Lebrikizumab:** Dermira, Inc. announced in January 2018 the initiation of a Phase 2b dose-ranging study evaluating the safety and efficacy of lebrikizumab in adult patients with moderate-to-severe AD. Lebrikizumab is a humanized monoclonal antibody designed to bind to IL-13. The randomized, double-blind, placebo-controlled, parallel-group Phase 2b study is designed to evaluate the safety and efficacy of lebrikizumab as monotherapy versus placebo and to establish the dosing regimen for a potential Phase 3 study in patients with moderate-to-severe AD. Results from the TREBLE study were published in *The Journal of the American Academy of Dermatology* in January 2018. TREBLE was a randomized, placebo-controlled, double-blind, Phase 2, proof-of-concept study designed to assess the safety and efficacy of lebrikizumab as add-on therapy to twice daily TCS for adult patients with moderate-to-severe AD. The primary endpoint was the percentage of patients achieving EASI-50 at week 12. Patients who received lebrikizumab 125mg administered every four weeks were significantly more likely to achieve EASI-50 (82.4%; P=0.026) compared with placebo (62.3%). Lebrikizumab was generally well-tolerated. There were no imbalances in proportions of patients reporting adverse events, serious adverse events, events leading to discontinuation, or overall infections when comparing all lebrikizumab-treated patients with placebo-treated patients.
- **Nemolizumab:** Chugai Pharmaceutical Co., Ltd. announced that the long-term data from a global Phase 2 study for nemolizumab was published in *The Journal of Allergy and Clinical Immunology Online* in May 2018. Nemolizumab is a humanized, anti-human, IL-31 receptor A monoclonal antibody. Nemolizumab improved pruritus, dermatitis, and sleep in adults with moderate-to-severe AD that was inadequately controlled by topical treatments in a Phase 2, 12-week, randomized, double-blind, placebo-controlled study (Part A). In the extension study (Part B), researchers sought to assess the long-term efficacy and safety of nemolizumab injected every 4 weeks (Q4W) or every 8 weeks (Q8W) in a 52-week, double-blind extension. Overall, 216 of 264 patients completed Part A, 191 entered Part B, and 131 patients completed Part B. In 153 patients randomized to nemolizumab in Part A, improvement from baseline in pruritus visual analog scale (VAS) score was maintained or increased from weeks 12 to 64, with the greatest improvement in the 0.5mg/kg Q4W group (percentage change from baseline at week 64: -73.0, -89.6, -74.7, and -79.1 in the 0.1, 0.5, 2.0mg/kg Q4W and 2.0mg/kg Q8W groups, respectively). Over 64 weeks, 83% to 89% of patients had one or more adverse events, with no new safety concerns identified. Nemolizumab for up to 64 weeks was efficacious and overall well tolerated in patients with moderate-to-severe AD who are inadequately controlled on topical therapies.
- **Fezakinumab:** Results from a Phase 2a, multicenter, randomized, placebo-controlled, double-blind study of fezakinumab, an anti-IL-22 monoclonal antibody, were published in *The Journal of the American Academy of Dermatology* in January 2018. A total of 60 patients were enrolled in the study to evaluate the safety and efficacy of fezakinumab in adults with moderate-to-severe AD. In the study, 40 patients were treated with intravenous (IV) fezakinumab monotherapy every 2 weeks for 10 weeks and 20 patients

received placebo. Follow-up assessments took place through week 20, and the primary endpoint was the Scoring Atopic Dermatitis (SCORAD) change from baseline at 12 weeks. At 12 weeks, the mean SCORAD decline was 13.8 ± 2.7 in the fezakinumab treatment group versus 8.0 ± 3.1 in the placebo group, which did not reach statistical significance (P=0.134). However, in patients with severe AD (baseline SCORAD ≥50), the SCORAD decline at 12 weeks was significantly greater with fezakinumab than with placebo (21.6 ± 3.8 vs. 9.6 ± 4.2, respectively; P=0.029). Improvements in body surface area were significantly greater in the fezakinumab group compared with the placebo group in the entire population (i.e., patients with moderate-to-severe AD; 12.4% ± 2.4% vs. 6.2% ± 2.7%, respectively; P=0.009). The most common adverse event was upper respiratory tract infection.

- **Upadacitinib:** AbbVie presented results from a Phase 2b dose-ranging study evaluating upadacitinib, an investigational, once-daily oral Janus kinase (JAK) 1-selective inhibitor, in adults with moderate-to-severe AD at the 2018 American Academy of Dermatology Annual Meeting in February. In September 2017, AbbVie announced positive top-line results from this Phase 2b study, including an evaluation of the primary endpoint – mean percentage change in EASI at week 16 versus placebo. Additional exploratory results showed a significant reduction of select symptoms of AD in upadacitinib patients, including reduction in itch at week 1 and improvement in the extent and severity of skin lesions at week 2 across all doses (30mg, 15mg, and 7.5mg once daily).

Other News:

- **October 2017:** According to a study published in *The Journal of the American Academy of Dermatology*, Eucrisa® (crisaborole) ointment appears to be safe for the long-term treatment of AD. The long-term safety was assessed from a multicenter, open-label, 48-week safety study of 517 patients 2 years of age and older with mild-to-moderate AD who continued crisaborole treatment after completing a 28-day Phase 3 pivotal study. The researchers found that during the pivotal study and the open-label trial, 65% of patients reported at least one treatment-emergent adverse event, most of which were mild (51.2%) or moderate (44.6%) and considered unrelated to treatment (93.1%). Treatment-related adverse events were reported in 10.2% of patients and most commonly included atopic dermatitis (3.1%), application site pain (2.3%), and application site infection (1.2%).
- **April 2018:** The National Institute for Health and Care Excellence (NICE) issued draft guidance rejecting Sanofi/Regeneron's Dupixent® (dupilumab) for the treatment of moderate-to-severe AD. The draft guidelines highlight that dupilumab is effective at treating moderate-to-severe AD following failure (or contraindication) of topical therapies and systemic immunosuppressants. However, NICE stated that cost-effectiveness estimates for dupilumab were uncertain and higher than normally considered an acceptable use of National Health Services (NHS) resources.

Recommendations

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

Eucrisa® (Crisaborole Ointment) Approval Criteria:

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

Clinical Exceptions for Children Not Meeting Age Restriction:

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

Utilization Details of AD Medications: Calendar Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
TACROLIMUS OIN 0.03%	620	440	$179,691.76	$9.57	$289.83	26.08%
ELIDEL CRE 1%	564	421	$188,946.26	$9.95	$335.01	27.42%
DOXEPIN HCL CRE 5%	164	117	$64,265.70	$13.18	$391.86	9.33%
TACROLIMUS OIN 0.1%	125	96	$31,922.14	$8.55	$255.38	4.63%
EUCRISA OIN 2%	97	76	$54,987.84	$18.54	$566.88	7.98%
DUPIXENT INJ 300MG/2ML	48	14	$168,353.84	$123.61	$3,507.37	24.43%
ZONALON CRE 5%	1	1	$625.26	$78.16	$625.26	0.09%
PROTOPIC OIN 0.03%	1	1	$253.64	$8.45	$253.64	0.04%
TOTAL	**1,620**	**1,129***	**$689,046.44**	**$13.58**	**$425.34**	**100.00%**

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

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Appendix I

Calendar Year 2017 Annual Review of Botulinum Toxins

Oklahoma Health Care Authority
July 2018

Current Prior Authorization Criteria

Botulinum Toxins Approval Criteria:

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

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

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

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

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

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

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

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

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

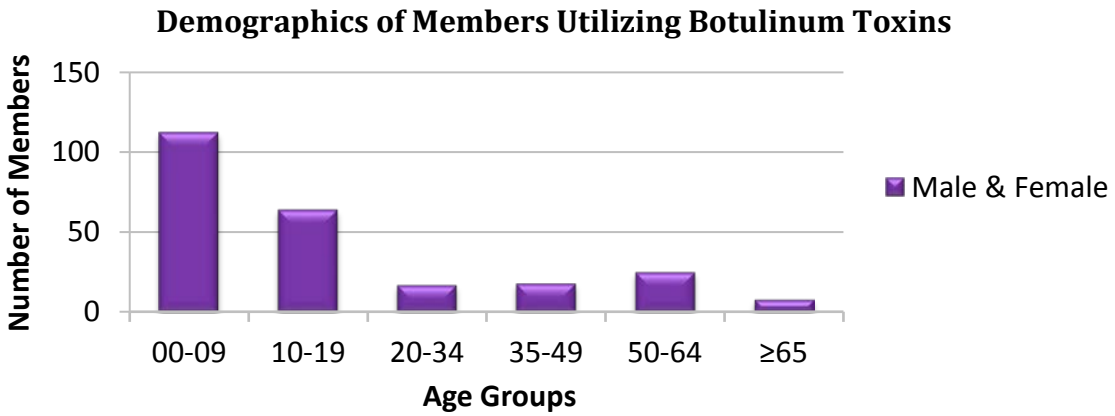
1. Diagnosis of neurogenic bladder including underlying pathological dysfunction subtype confirmed by:
    a. Urodynamic studies to determine pathology and serve to provide objective evidence of bladder and external sphincter function; and
    b. A diary of fluid intake, incontinence, voiding, and catheterization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

Utilization of Botulinum Toxins: Calendar Year 2017

Comparison of Calendar Years: Botulinum Toxins

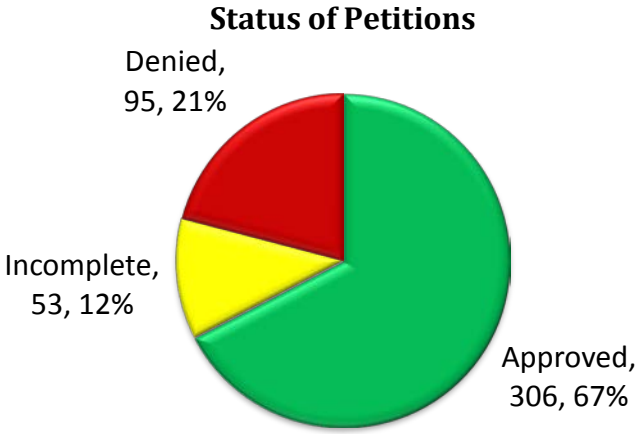
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Claims/ Member
2016	208	366	$516,394.50	$1,410.91	1.8
2017	240	435	$618,054.02	$1,420.81	1.8
% Change	**15.38%**	**18.85%**	**19.69%**	**0.70%**	**0.00%**
Change	**32**	**69**	**$101,659.52**	**$9.90**	**0**

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



Prior Authorization of Botulinum Toxins

There were 454 prior authorization requests submitted for botulinum toxins during calendar year 2017. The following chart shows the status of the submitted petitions for calendar year 2017.



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

New FDA Approved Indication(s):

- **June 2017:** The FDA approved Dysport® (abobotulinumtoxinA) for the treatment of lower limb spasticity in adult patients. Dysport® was first FDA approved in 2009 for the treatment of cervical dystonia in adult patients, then in 2015 for the treatment of upper limb spasticity in adult patients, and then in 2016 for the treatment of lower limb spasticity in pediatric patients age 2 years and older. The current approval criteria and covered diagnosis codes for botulinum toxins include lower limb spasticity.

News:

- **May 2018:** According to a new study, botulinum toxins may be the key to halting invasive infections, like necrotizing fasciitis. Although best known for causing strep throat, scarlet fever, and impetigo, *Streptococcus pyogenes* (*S. pyogenes*) are also known to cause necrotizing fasciitis, a rare, flesh-eating disease that could potentially be

deadly if not diagnosed early and treated promptly. Early symptoms of necrotizing fasciitis include localized pain, fever, chills, fatigue, and vomiting. In a recent study funded by grants from the National Institutes of Health and published in the journal *Cell*, Harvard Medical School researchers investigated the intense pain experienced by individuals with necrotizing fasciitis, which usually occurs before any visual signs of infection. They found that *S. pyogenes* target neurons and produce a toxin called streptolysin S (SLS), which activates certain pain-related neurons, leading to extreme pain. The toxin also disrupts communication between the nervous system and the immune system, essentially lowering the body's immune response and ability to kill the bacteria. In the study, the researchers injected mice with bacterial strains from patients with invasive strep infections. They found that mice infected with bacteria genetically modified to lack SLS did not show signs of pain or develop invasive infections. When infected with bacteria re-engineered to produce the toxin, the mice developed full-blown disease. Researchers then administered a neutralizing antibody to inactivate SLS, and the mice displayed fewer signs of pain. In addition, researchers tested botulinum neurotoxin A to block nerve signals. The botulinum controlled the spread of infection, and mice injected with the nerve block one week before being infected with *S. pyogenes* developed only minimal wounds. These findings reveal a surprising new role of neurons in the development of this disease and point to promising countermeasures that warrant further exploration. However, since this study only looked at mice, similar research needs to be conducted on larger animals and human patients.

Pipeline:

- **November 2017:** An attempt to reduce atrial fibrillation following cardiac surgery by injecting botulinum toxin into epicardial fat pads missed its clinical trial goal. One week after cardiac surgery, 36.5% of patients treated with botulinum toxin experienced atrial fibrillation compared with 47.8% of the patients treated with placebo, an 11% absolute reduction in risk that failed to reach statistical significance (P=0.18). The trial included 130 patients, 63 who were treated with botulinum toxin and 67 who received saline injections. Despite missing its clinical trial goal, researchers are interested in studying this potential solution further in larger scale clinical trials, knowing that atrial fibrillation is one of the most common adverse effects that occurs after cardiac surgery and is associated with increased morbidity, increased length of stay in the hospital, and increased mortality. No significant safety signals related to epicardial botulinum injection were observed.
- **May 2018:** Evolus, Inc. received a complete response letter (CRL) from the FDA related to its pending Biologics License Application (BLA) for DWP-450 (prabotulinumtoxinA) for the treatment of glabellar lines in adult patients. This indication is considered cosmetic and if FDA approved, would not be a covered indication by SoonerCare. In the CRL, deficiencies cited by the FDA were isolated to items related to Chemistry, Manufacturing, and Controls (CMC) processes; no deficiencies were related to clinical or non-clinical matters. Evolus expects to respond with a complete submission to the FDA within 90 days and hopes to bring DWP-450 to the market by spring 2019.

Recommendations

The College of Pharmacy recommends updating the current prior authorization criteria for Botox® (onabotulinumtoxinA) for the prevention of migraine headaches, based on the FDA approved indication, the International Classification of Headache Disorders (ICHD-3)[7] diagnostic criteria for chronic migraine and for medication overuse headache (MOH), and current net costs (changes noted in red):

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

1. Non-migraine medical conditions known to cause headache have been ruled out and/or have been treated. This includes, but is not limited to:
    a. Increased intracranial pressure (e.g., tumor, pseudotumor cerebri, central venous thrombosis); or
    b. Decreased intracranial pressure (e.g., post-lumbar puncture headache, dural tear after trauma); and
2. Migraine headache exacerbation secondary to other medical conditions or medication therapies have been ruled out and/or treated. This includes, but is not limited to:
    a. Hormone replacement therapy or hormone-based contraceptives; and
    b. Chronic insomnia; and
    c. Obstructive sleep apnea; and
3. Member has no contraindications to Botox® injections; and
4. FDA indications are met:
    a. Member is 18 years of age or older; and
    b. Member has documented chronic migraine headaches:
        i. Frequency of 15 or more headache days per month with 8 or more migraine days per month and occurring for more than 3 months; and
        ii. Duration of four hours of headache per day or longer; and
5. The member has failed medical migraine preventative therapy including at least ~~three~~ two agents ~~in three or more categories~~ with different mechanisms of action. This includes, but is not limited to:
    a. Select antihypertensive therapy (e.g., beta-blockers); or
    b. Select anticonvulsant therapy; or
    c. Select antidepressant therapy [e.g., tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI)]; and
6. Member is not frequently taking medications which are known to cause medication overuse headaches (MOH or rebound headaches) in the absence of intractable conditions known to cause chronic pain. MOH are a frequent cause of chronic headaches. A list of prescription or non-prescription medications known to cause MOH includes, but is not limited to:
    a. Decongestants (alone or in combination products) (≥10 days/month for >3 months); and
    b. Combination analgesics containing caffeine and/or butalbital (~~>5~~ ≥10 days/month for >3 months); and
    c. Opioids (≥10 days/month for >3 months); and

d. Analgesic medications including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) (≥15 days/month for >3 months); and
e. Ergotamine-containing medications (~~>8~~ ≥10 days/month for >3 months); and
f. Triptans (~~>8~~ ≥10 days/month for >3 months); and

7. Member is not taking any medications that are likely to be the cause of the headaches; and
8. Member must have been evaluated within the last six months by a neurologist for chronic migraine headaches and Botox® recommended as treatment (not necessarily prescribed or administered by a neurologist); and
9. Members who smoke or use tobacco products will not be approved.

Utilization Details of Botulinum Toxins: Calendar Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
ONABOTULINUMTOXINA PRODUCTS						
BOTOX® (J0585)	424	236	$610,081.92	$1,438.87	1.8	98.71%
SUBTOTAL	**424**	**236**	**$610,081.92**	**$1,438.87**	**1.8**	**98.71%**
RIMABOTULINUMTOXINB PRODUCTS						
MYOBLOC® (J0587)	6	3	$5,706.00	$951.00	2	0.92%
SUBTOTAL	**6**	**3**	**$5,706.00**	**$951.00**	**2**	**0.92%**
INCOBOTULINUMTOXINA PRODUCTS						
XEOMIN® (J0588)	4	2	$1,770.50	$442.63	2	0.29%
SUBTOTAL	**4**	**2**	**$1,770.50**	**$442.63**	**2**	**0.29%**
ABOBOTULINUMTOXINA PRODUCTS						
DYSPORT® (J0586)	1	1	$495.60	$495.60	1	0.08%
SUBTOTAL	**1**	**1**	**$495.60**	**$495.60**	**1**	**0.08%**
TOTAL	**435**	**240***	**$618,054.02**	**$1,420.81**	**1.8**	**100%**

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

[1] Ipsen News Release: Ipsen Announces FDA Approval of Dysport® (AbobotulinumtoxinA) for the Treatment of Lower Limb Spasticity in Adults. Available online at: https://www.ipsen.com/media/press-relases/ipsen-announces-fda-approval-dysport-abobotulinumtoxina-treatment-lower-limb-spasticity-adults/. Issued 06/16/2017. Last accessed 06/20/2018.
[2] Keet E. Botox Could Be Key to Halting Invasive Infections Like Necrotizing Fasciitis. *Rare Disease Report.* Available online at: https://www.raredr.com/news/botox-could-be-key-to-halting-invasive-infections-like-necrotizing-fasciitis. Issued 05/28/2018. Last accessed 06/19/2018.
[3] Pinho-Ribeiro FA, Baddal B, Haarsma R, et al. Blocking Neuronal Signaling to Immune Cells Treats Streptococcal Invasive Infection. *Cell.* 2018; 173(5):1083-1097.
[4] Susman E. AHA: Botulinum Toxin Misses Mark in Stopping Afib. *MedPage Today.* Available online at: https://www.medpagetoday.com/meetingcoverage/aha/69321. Issued 11/15/2017. Last accessed 06/19/2018.
[5] Study Suggests Botox May Help Prevent AFib After Heart Surgery. *American Heart Association News.* Available online at: https://news.heart.org/study-suggests-botox-may-one-day-help-prevent-afib-heart-surgery/. Issued 11/15/2017. Last accessed 06/19/2018.
[6] Evolus, Inc. News Release: Evolus Announces Progress with DWP-450 Regulatory Submissions. Available online at: https://investors.evolus.com/news-releases/news-release-details/evolus-announces-progress-dwp-450-regulatory-submissions. Issued 05/16/2018. Last accessed 06/19/2018.
[7] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd Edition (ICHD-3). *Cephalalgia*. 2018; 38(1):1-211.

Appendix J

Calendar Year 2017 Annual Review of Opioid Analgesics and Opioid Medication Assisted Treatment (MAT) Medications and 30-Day Notice to Prior Authorize Apadaz® [Benzhydrocodone/ Acetaminophen(APAP)], Lucemyra™ (Lofexidine), and Sublocade™ [Buprenorphine Extended-Release (ER) Injection]

Oklahoma Health Care Authority
July 2018

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

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

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

◊Brand name preferred.

- Tier-1 products are covered with no prior authorization necessary.
- Members with an oncology-related diagnosis are exempt from the prior

authorization process, and do not require pain contracts.

- Only one long-acting and one-short acting agent can be used concurrently. Short-acting, solid dosage formulation products are limited to a quantity of four units per day or a quantity of 120 units per 30 days.
- An age restriction applies on oral liquid narcotic analgesic products for all members older than 12 years of age and oral solid dosage forms for all members younger than 10 years of age.
- An age restriction for all tramadol and codeine products (both liquid and solid dosage formulations) for members younger than 12 years of age applies. Members younger than 12 years of age require prior authorization approval for reimbursement of these products. Authorization requires a patient-specific, clinically significant reason for use of these products despite the medication being contraindicated for the member's age.

Opioid Analgesics Tier-2 Approval Criteria:

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

Opioid Analgesics Tier-3 Approval Criteria:

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

Opioid Analgesics Special Prior Authorization (PA) Approval Criteria:

1. Actiq®, Fentora®, Onsolis®, Abstral®, Lazanda®, and Subsys® are approved for oncology-related diagnoses only.
2. Unique Strengths of Hydrocodone/Acetaminophen (APAP) Approval Criteria:
    a. A patient-specific, clinically significant reason why the member cannot use generic Norco® (hydrocodone/APAP 5/325mg, 7.5/325mg, or 10/325mg).
3. ConZip® [Tramadol Extended-Release (ER) Capsules] Approval Criteria:
    a. A patient-specific, clinically significant reason why the member cannot use the ER tablet formulation.
4. Xartemis® XR (Oxycodone/APAP ER Tablets) Approval Criteria:
    a. An acute pain condition requiring around-the-clock opioid treatment; and
    b. A patient-specific, clinically significant reason for all of the following:
        i. Why the member cannot use any other opioid medication for treatment of acute pain; and
        ii. Why the member requires a long-acting medication for an acute pain condition; and
        iii. Why the member cannot use Oxycontin® (oxycodone ER) and over-the-counter (OTC) APAP individual products in place of this combination product; and

c. A quantity limit of four tablets per day will apply with a maximum approval duration of 10 days; and
d. The member must not exceed 3,250mg of APAP per day from all sources; and
e. Tier structure rules still apply.

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

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

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

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

High-Dose Buprenorphine Products Approval Criteria:

1. Each request for greater than 24mg bioequivalent buprenorphine per day will be evaluated on a case-by-case basis.
2. A taper schedule, dates of an attempted taper with reason for failure, or a patient-specific, clinically significant reason why a taper schedule or attempt is not appropriate for the member should be documented on the prior authorization request; and
3. Opioid urine drug screens should be submitted with high-dose requests that plan to continue high-dose treatment longer than the duration of one month.
    a. Urine drug screens must show the absence of opioid medications other than buprenorphine products for continued approval; or
    b. Prescriber must document a patient-specific reason the member should continue therapy, reason for opioid use, and document a plan for member to discontinue opioid use; and
4. Symptoms associated with withdrawal at lower doses or symptoms requiring high doses should be listed on the prior authorization request; and
5. Each approval will be for the duration of one month. If urine drug screen and other documentation are submitted indicating high-dose therapy is necessary, an approval can be granted for the duration of three months.
6. Continued high-dose authorization after the three-month approval will require a new (recent) urine drug screen.

Probuphine® (Buprenorphine Implant) Approval Criteria:

1. An FDA approved indication of maintenance treatment of opioid dependence; and
2. Members must be currently on a maintenance dose of 8mg per day or less of a Subutex® or Suboxone® sublingual tablet or its transmucosal buprenorphine product equivalent; and
3. Member must have been stable on current transmucosal buprenorphine dose (of 8mg per day or less) for three months or longer without any need for supplemental dosing or adjustments; and
4. Members must have had no positive urine toxicology results or paid claims for opioids within the last three months. Concomitant treatment with opioids (including tramadol) will be denied; and
5. Probuphine® must be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a Drug Enforcement Agency (DEA) X number; and
6. Prescribers must verify they have considered the following factors in determining clinical stability and suitability for Probuphine®:
    a. Period free from illicit opioid drug use
    b. Stability of living environment
    c. Participation in a structured activity/job
    d. Consistency in participation in recommended behavioral therapy/peer support program
    e. Consistency in compliance with clinic visit requirements
    f. Minimal to no desire or need to use illicit opioids

g. Period without episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions
h. Social support system

7. The prescriber must verify enrollment in the Probuphine® Risk Evaluation and Mitigation Strategy (REMS) program; and
8. Approvals will be for one kit (four implants) per six months. Reauthorizations for an additional six months may be granted if the member does not have ongoing use of supplemental dosing with transmucosal buprenorphine or opioid analgesics while utilizing Probuphine®.

Utilization of Opioid Analgesics and MAT Medications: Calendar Year 2017

Comparison of Calendar Years: Opioid Analgesics

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	116,548	416,580	$18,063,367.59	$43.36	$2.26	29,362,576	7,996,605
2017	105,824	371,526	$16,451,977.07	$44.28	$2.29	26,186,505	7,194,111
% Change	**-9.20%**	**-10.80%**	**-8.90%**	**2.10%**	**1.30%**	**-10.80%**	**-10.00%**
Change	**-10,724**	**-45,054**	**-$1,611,390.52**	**$0.92**	**$0.03**	**-3,176,071**	**-802,494**

*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
2016	1,793	13,140	$4,334,565.30	$329.88	$12.65	708,439	342,536
2017	2,196	15,805	$4,710,665.49	$298.05	$11.35	848,919	415,166
% Change	**22.50%**	**20.30%**	**8.70%**	**-9.60%**	**-10.30%**	**19.80%**	**21.20%**
Change	**403**	**2,665**	**$376,100.19**	**-$31.83**	**-$1.30**	**140,480**	**72,630**

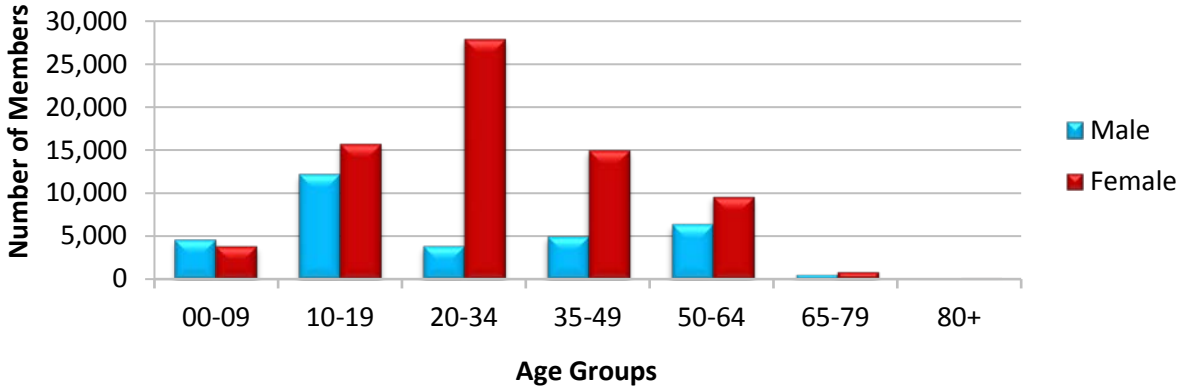
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Does not include Butrans® or Belbuca® claims.

- Aggregate drug rebates collected during calendar year 2017 for opioid analgesics and MAT medications: $9,220,339.37[Δ]
- Please note, due to new federal regulations, a new pricing methodology for pharmacy claims reimbursement was implemented by SoonerCare on January 3, 2017. Ingredient reimbursement changed from an estimated acquisition cost (EAC) to an actual acquisition cost (AAC). In addition, the professional dispensing fee increased from $3.60 in 2016 to $10.55 effective January 2017; professional dispensing fees are included in the reimbursement totals in the following report. The impact of the pricing methodology and dispensing fee change are estimated to be budget neutral. This change in reimbursement

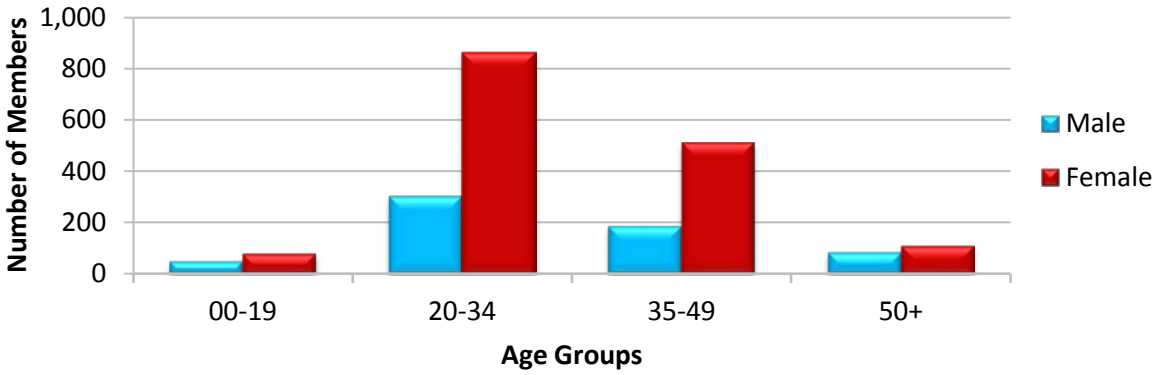
[Δ] Important considerations: Aggregate drug rebates are based on the date the claim is paid rather than the date dispensed. Claims data are based on the date dispensed.

should be considered when evaluating reimbursement changes from year to year. Medications with a very low cost per claim and large volume of claims will appear to increase in price due to the increase in dispensing fee; however, these increases will be neutralized by changes in ingredient reimbursement for higher cost medications.

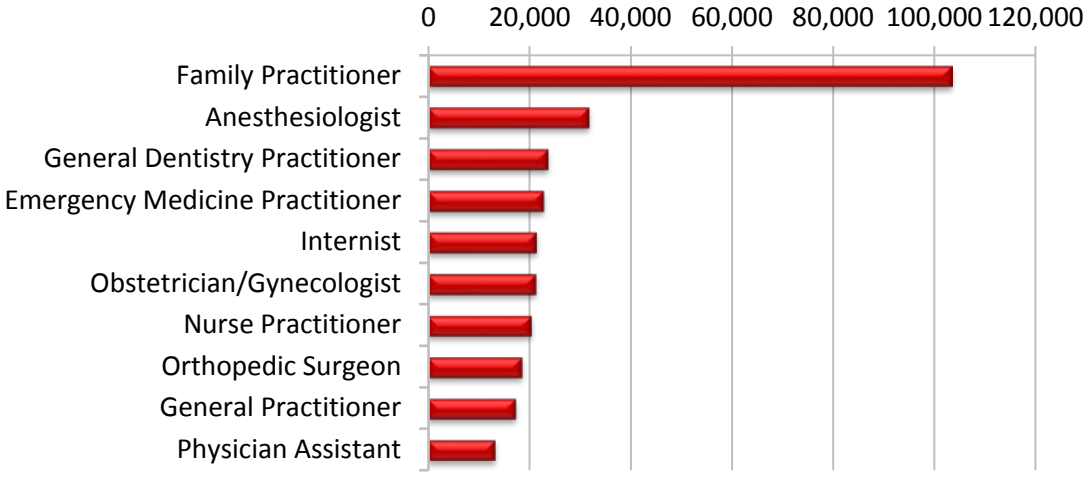
Demographics of Members Utilizing Opioid Analgesics



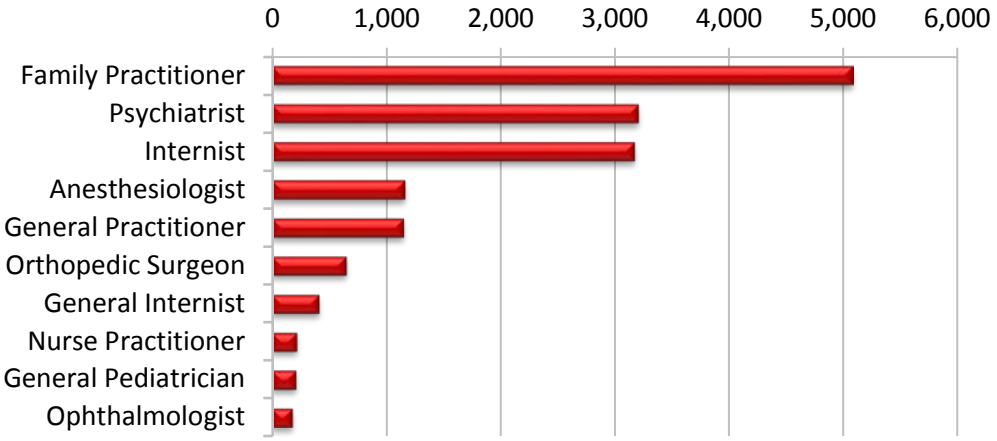
Demographics of Members Utilizing MAT Medications



Top Prescriber Specialties of Opioid Analgesics by Number of Claims



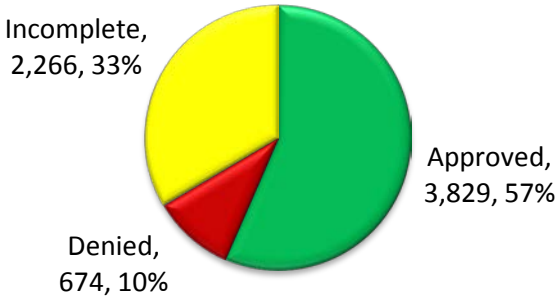
Top Prescriber Specialties of MAT Medications by Number of Claims



Prior Authorization of Opioid Analgesics and MAT Medications

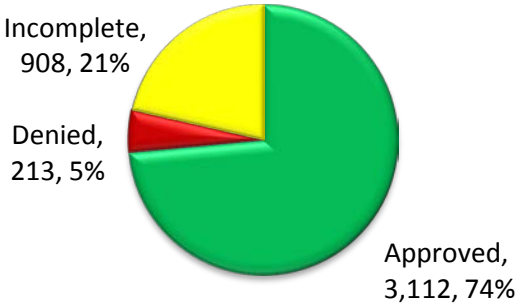
There were 6,769 prior authorizations submitted for the opioid analgesics category during calendar year 2017. Computer edits are in place to detect diagnosis, quantities/day supply, and lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.

Status of Petitions



There were 4,233 prior authorizations submitted for MAT medications during calendar year 2017. 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.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38]

Anticipated Patent Expiration(s):

- Abstral® [fentanyl sublingual (SL) tablets]: September 2019
- Probuphine® (buprenorphine implants): April 2024
- Lazanda® (fentanyl nasal spray): October 2024
- Oxaydo® [oxycodone immediate-release (IR) tablets]: March 2025
- Nucynta® (tapentadol IR tablets): June 2025
- Troxyca® ER [oxycodone/naltrexone ER capsules]: December 2027
- Fentora® (fentanyl buccal tablets): June 2028
- MorphaBond™ (morphine ER tablets): August 2028
- RoxyBond™ (oxycodone IR tablets): August 2028
- Nucynta® ER (tapentadol ER tablets): September 2028
- Vantrela™ ER (hydrocodone ER tablets): July 2029
- Embeda® (morphine/naltrexone ER tablets): November 2029
- Subsys® (fentanyl SL spray): April 2030
- Apadaz® [benzhydrocodone/APAP IR tablets]: February 2031
- Hysingla® ER (hydrocodone bitartrate ER tablets): December 2031
- Sublocade™ (buprenorphine ER injection): January 2032
- Xartemis® XR (oxycodone/APAP ER tablets): May 2032
- Zubsolv® (buprenorphine/naloxone SL tablets): September 2032
- Belbuca® (buprenorphine ER buccal films): December 2032
- Arymo® ER (morphine ER tablets): July 2033
- Zohydro® ER (hydrocodone bitartrate ER capsules): September 2034
- Bunavail® (buprenorphine/naloxone buccal films): April 2035
- Xtampza® ER (oxycodone ER capsules): September 2036

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

- **November 2017:** Sublocade™ (buprenorphine ER injection)
- **February 2018:** Apadaz® (benzhydrocodone/APAP IR tablets)
- **May 2018:** Lucemyra™ (lofexidine tablets)
- **June 2018:** Generic formulations of Suboxone® (buprenorphine/naloxone film)

Oklahoma Legislative Update(s):

- **May 2018:** Oklahoma Senate Bill (SB) 1446 was signed into law and places a 7-day limit on initial opioid prescriptions. While enforcement and other details of the law are currently pending, many pharmacies and providers are already implementing these limitations.

Guideline Recommendation(s):

- **May 2018:** The American College of Obstetricians and Gynecologists (ACOG) wrote a committee opinion recommending that pain management for postpartum patients be individualized in a stepwise approach. APAP and nonsteroidal anti-inflammatory drugs (NSAIDs) were recommended first-line for vaginal births followed by a “milder opioid” if NSAIDs are inadequate. For cesarean birth, opioids could be potentially used in combination with APAP or an NSAID. Additional recommendations included avoiding the

use of codeine and tramadol during breastfeeding and that the duration of opioid prescriptions be for the shortest reasonable course of time.

FDA and Drug Enforcement Administration (DEA) Update(s):

- **September 2017:** The FDA issued a drug safety communication advising that opioid addiction medications (buprenorphine and methadone) not be withheld from patients taking benzodiazepines or other medications that can depress the central nervous system (CNS). The FDA indicated that while concomitant use of CNS depressants and MAT medications may increase the risk of overdose, the harm caused by untreated opioid addiction can outweigh these risks. The FDA advised that careful medication management by health care professionals can reduce these risks and required information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of MAT medications and benzodiazepines together.
- **November 2017:** The FDA issued guidance to assist manufacturers in the development of generic versions of approved abuse-deterrent opioids including the type of studies companies should conduct to demonstrate that the generic formulation is no less abuse-deterrent than the brand formulation.
- **December 2017:** The FDA Commissioner Scott Gottlieb, MD, proposed the idea of creating a corporate-sponsored, nationwide prescription drug monitoring program as a potential option to prevent opioid abuse. The idea was one of several proposed at an FDA workshop intended to enhance opioid safety.
- **January 2018:** The DEA expanded access for nurse practitioners and physician assistants to become prescribers and dispensers of buprenorphine for opioid use disorders. Under the new expanded access, nurse practitioners and physician assistants are eligible to apply for a buprenorphine waiver provided they are licensed under state law to prescribe Schedule III, IV, or V medications for the treatment of pain and that they receive at least 24 hours of initial training.
- **January 2018:** The FDA issued a drug safety communication requiring label changes that limit the use of prescription opioid cough and cold medicines containing codeine or hydrocodone to adults 18 years of age and older. The FDA indicated that the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death with these medicines outweigh the benefits in patients younger than 18 years of age. Opioid cough and cold medicines are not a covered SoonerCare benefit.
- **February 2018:** The FDA extended the Risk Evaluation and Mitigation Strategy (REMS) for opioid analgesics to include IR opioid analgesics in addition to ER and long-acting (LA) opioid analgesics. The modified REMS will include additional training for health care professionals regarding educational content in pain management, including the principles of acute and chronic pain management, non-pharmacologic treatments for pain, and pharmacologic treatments for pain (both non-opioid analgesics and opioid analgesics).
- **February 2018:** The DEA placed all illicit fentanyl analogues not already regulated by the Controlled Substances Act into Schedule I, the category for substances with no currently accepted medical use. With the new scheduling, anyone who possesses, imports, distributes, or manufactures any illicit fentanyl analogue will be subject to criminal prosecution.

- **June 2018:** The FDA approved a wearable device for the treatment of opioid withdrawal symptoms. The auricular neurostimulator, Drug Relief®, manufactured by DyAnsys, Inc., provides percutaneous electrical nerve field stimulation for up to 5 days to reduce agitation, anxiety, depression, and opiate cravings.

Centers for Medicare and Medicaid Services (CMS) Update(s):

- **February 2018:** CMS proposed that beginning in 2019, initial opioid prescriptions for acute pain be limited to 7 days and no more than 90 morphine milligram equivalent (MME); in addition, CMS suggested that Medicare Part D plans monitor patients taking opioids with "potentiators" such as Neurontin® (gabapentin) and Lyrica® (pregabalin). CMS also proposed a quality measure to track how well Part D plans flag concurrent use of opioids and benzodiazepines.

News:

- **January 2018:** An Australian study of opioid sales data, an illicit drug reporting system, ambulance and emergency department records, opioid treatment and help-seeking records, and a cohort of 606 injection drug users found that the introduction of an abuse-deterrent formulation of oxycodone had no impact on reducing hospital admissions, emergency department visits, or overdoses. However, the abuse-deterrent formulation introduction was associated with reduced oxycodone tampering among injection drug users.
- **February 2018:** The Institute for Safe Medication Practices (ISMP) revealed that insulin and opioids were the two classes of drugs most frequently linked with in-hospital mistakes reported to ISMP in 2017.
- **March 2018:** A study of 240 patients published in *The Journal of the American Medical Association (JAMA*) found non-opioid medications to be equally efficacious as opioid medications in treating pain in people with chronic back pain or pain from hip or knee osteoarthritis. In the study, primary care clinics using the 7-item Brief Pain Inventory (BPI) interference scale and the 4-item pain intensity BPI severity scale found at 12 months, the mean BPI interference was 3.4 in the opioid group and 3.3 in the non-opioid group [difference 0.1; 95% confidence interval (CI) -0.5 to 0.7]. Pain intensity was significantly better in the non-opioid group, at 3.5 compared with 4.0 in the opioid group (difference 0.5; 95% CI 0.0 to 1.0). Additionally, medication-related symptoms were more common in the opioid group.
- **April 2018:** The Institute for Clinical and Economic Review (ICER) announced plans to develop a report assessing comparative clinical effectiveness and value of MAT options for opioid use disorder. The report will be the subject of a public meeting of the New England Comparative Effectiveness Public Advisory Council (CEPAC) in November of 2018.
- **May 2018:** A study of 17,568 Massachusetts overdose patients between 2012 and 2014 published in the *Annals of Internal Medicine* found that treating opioid overdose survivors with buprenorphine or methadone resulted in a 40% to 60% decline in mortality after 1 year. The study also found that only 3 in 10 overdose survivors received medication for opioid use disorder in the year after overdose.
- **May 2018:** The American Medical Association (AMA) released a report indicating that opioid prescriptions had decreased by 22.2% from 2013 to 2017. The AMA also indicated

that prescribers were checking the PMP more often, citing a 121% increase from 2016 to 2017.

- **June 2018:** A retrospective cohort study of 2,492 satisfaction scores for patients who were prescribed opioids for chronic pain for at least 6 months from 2009 to 2014 found that despite reducing doses of opioids, overall satisfaction was maintained in most encounters (86.4%).
- **June 2018:** A 24-week randomized clinical trial of 428 adults with opioid use disorder found subcutaneous (sub-Q) buprenorphine noninferior to SL buprenorphine/naloxone after analysis of opioid-negative urine samples (Sub-Q: 35.1% vs. SL: 28.4%).
- **June 2018:** A study published in *JAMA* found that a total of 7.0% of 369,139 prescribers who prescribed opioids under Medicare Part D in 2015 had received nonresearch opioid-related payments in 2014. Prescribers who did not receive opioid-related payments had fewer opioid claims in 2015 than in 2014 while prescribers who did receive opioid-related payments had an increase in opioid claims. Any opioid-related payments in 2014 were associated with 9.3% (95% CI 8.7% to 9.9%) more opioid claims in 2015 compared with prescribers who did not receive opioid-related payments.
- **June 2018:** A study published in *JAMA* found that opioids were linked to 1 out of every 65 deaths in the United States during 2016. Those in the 25 to 34 year old age group had the highest rate of opioid-linked death amounting to 1 out of 5 deaths.
- **June 2018:** Dr. Reddy's generic formulation of Suboxone® (buprenorphine/naloxone film) has been blocked from marketing by a United States district court after Indivior, the maker of Suboxone®, filed a temporary restraining order. Appeal and patent litigation is ongoing.

Pipeline:

- **September 2017:** The FDA issued a Complete Response Letter (CRL) to Intellipharmaceutics for the company's product, Rexista® (oxycodone ER). Rexista® is formulated with abuse-deterrent properties including a blue dye that is released when abused via the intranasal route. The FDA requested additional studies to assess the abuse-deterrent properties of Rexista® by the oral and nasal routes of administration.
- **October 2017:** AcelRx Pharmaceuticals received a CRL from the FDA for Dsuvia™ (sufentanil SL tablet), an investigational SL opioid analgesic. The FDA requested additional safety data to assess the maximum amount described in the proposed labeling and the FDA requested changes to the label to ensure proper administration of the tablet with the single-dose applicator. AcelRX indicated they intend to resubmit the New Drug Application (NDA) after working with the FDA to address their concerns.
- **January 2018:** Elite Pharmaceuticals, Inc. reported positive results from a pharmacokinetic study of SequestOx™ (oxycodone), an abuse-deterrent formulation of oxycodone. SequestOx™ achieved similar drug concentrations to the reference drug Roxicodone® (oxycodone), a feat not achieved by previously tested formulations of SequestOx™. Elite intends to discuss the pharmacokinetic study and the requirements for an NDA submission with the FDA.
- **February 2018:** An FDA advisory panel voted against approving Hydexor™ (hydrocodone 7.5mg/APAP 325mg/promethazine 12.5mg). Some concerns expressed by the committee included the lack of data for use in the elderly, plans for abuse and misuse deterrence, and the inflexibility of the single-dose product.

- **May 2018:** Braeburn Pharmaceuticals resubmitted an NDA for CAM2038, an investigational, long-acting, sub-Q buprenorphine injection for the treatment of patients with opioid use disorder. Previously in January 2018, Braeburn received a CRL from the FDA for CAM2038 requesting more data for approval.
- **May 2018:** Insys Therapeutics, Inc. announced that an FDA advisory panel voted not to recommend approval of the company's NDA for a SL spray formulation of buprenorphine as a treatment for moderate-to-severe, acute pain.
- **June 2018:** The Anesthetic and Analgesic Drug Products FDA Advisory Committee voted against recommending approval of Remoxy® ER (oxycodone ER capsules). The Committee voted 14 to 3 that data on the efficacy, safety, and risk-benefit profile of Remoxy® ER did not support approval. Remoxy® ER has been formulated with a gel that is intended to deter tampering and alternative routes of abuse such as injection, snorting, and smoking.

Apadaz® (Benzhydrocodone/APAP Tablets) Product Summary[39,40]

Indication(s): Apadaz® (benzhydrocodone/APAP tablets) is a combination of benzhydrocodone, a prodrug of the opioid agonist hydrocodone, and APAP, and is indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Dosing:

- Apadaz® is available as IR oral tablets containing 6.12mg benzhydrocodone (equivalent to 6.67mg benzhydrocodone hydrochloride) and 325mg APAP.
- Initial recommended dosing is 1 or 2 tablets every 4 to 6 hours as needed for pain. Dosages should not exceed 12 tablets in a 24-hour period.
- It is recommended that if switching from immediate-release hydrocodone bitartrate/ APAP, 6.12mg/325mg Apadaz® should be substituted for 7.5mg/325mg hydrocodone bitartrate/APAP.
- Dosages of Apadaz® should be adjusted according to the severity of the pain and the response of the patient.

Boxed Warning: Addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; hepatotoxicity; cytochrome P450 3A4 interaction; risks from concomitant use with benzodiazepines or other CNS depressants

Efficacy: The approval of Apadaz® was based on pharmacokinetic studies with hydrocodone/ibuprofen, tramadol/APAP, and hydrocodone/APAP in which Apadaz® demonstrated exposure to hydrocodone and APAP that is expected to result in therapeutic effects equivalent to currently approved IR hydrocodone/APAP combination products.[40]

Abuse Deterrence Studies:

- In Vitro Testing: In vitro physical and chemical manipulation studies were performed to evaluate different methods used to extract and convert benzyhydrocodone to hydrocodone for the purpose of preparing Apadaz® for abuse by the intravenous (IV) route or by smoking. The efficiency of extracting benzhydrocodone from Apadaz® was similar compared to the efficiency of extracting hydrocodone from the non-abuse-deterrent hydrocodone/APAP control. Further conversion (hydrolysis) of benzhydrocodone to

hydrocodone in vitro is a difficult process. Overall, these studies showed no advantage for Apadaz® over the hydrocodone/APAP control.

- Oral Clinical Abuse Potential Study: An oral abuse potential study was conducted in 71 subjects who were recreational opioid users. Treatment arms included Apadaz® (4, 8, and 12 tablets), hydrocodone/APAP (4, 8, and 12 tablets, each containing 4.54mg hydrocodone/325mg APAP), and placebo. The respective dosage strengths for Apadaz® and hydrocodone/APAP contained equimolar amounts of hydrocodone. There were no statistically significant differences nor any clinically meaningful differences between Apadaz® and the hydrocodone/APAP control for the pre-specified primary endpoint of maximal score (Emax) for "drug liking" on a visual analog scale (VAS) or secondary endpoints of Emax for "high" on a VAS and "take drug again" on a VAS. The results do not support a finding that Apadaz® can be expected to deter abuse by the oral route of administration.
- Intranasal Clinical Abuse Potential Study: An intranasal abuse potential study was conducted in 46 subjects who were recreational opioid users. Treatment arms included intranasal crushed and oral Apadaz® (2 tablets), intranasal crushed and oral hydrocodone/APAP (2 tablets, each containing 4.54mg hydrocodone/325mg APAP), and intranasal placebo powder. The respective dosage strengths for Apadaz® and hydrocodone/APAP contained equimolar amounts of hydrocodone. There were numerically small but not statistically significant differences between Apadaz® and the hydrocodone/APAP control observed for the pre-specified primary endpoint, Emax for "drug liking" on a VAS, and the secondary endpoints of Emax for "high" on a VAS and "take drug again" on a VAS. The results do not support a finding that Apadaz® can be expected to deter abuse by the intranasal route of administration.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 14 Days
Apadaz® (benzhydrocodone/APAP tablets) 6.12mg/325mg	**Not Available**	**Not Available**
hydrocodone/APAP tablets 7.5mg/325mg	$0.14	$7.84

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 recommended dose when switching from immediate-release hydrocodone bitartrate/APAP and recommended dosing of 1 tablet every 6 hours as needed for pain (a quantity limit of 120 tablets per 30 days applies).
Unit = tablet; APAP = acetaminophen

Lucemyra™ (Lofexidine Tablets) Product Summary[41,42]

Indication(s): Lucemyra™ (lofexidine tablets) is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

Dosing:

- Lucemyra™ is supplied as oral tablets containing 0.18mg lofexidine.
- The usual recommended dosage of Lucemyra™ is 3 tablets taken orally 4 times daily at 5- to 6-hour intervals. Lucemyra™ treatment may be continued for up to 14 days with dosing guided by symptoms.
- Lucemyra™ should be discontinued with a gradual dose reduction over 2 to 4 days.

- Dosage adjustments are recommended based on the degree of renal or hepatic impairment.

Efficacy: The efficacy of Lucemyra™ was evaluated in two randomized, double-blind, placebo-controlled trials in patients meeting Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone).

- Study 1: The first part of the study was an inpatient, randomized, double-blind, placebo-controlled design consisting of 7 days of inpatient treatment (days 1 to 7) with Lucemyra™ 2.16mg total daily dose (0.54mg four times daily; n=229), Lucemyra™ 2.88mg total daily dose (0.72mg four times daily; n=222), or matching placebo (n=151). Patients also had access to a variety of support medications for withdrawal symptoms (e.g., guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, APAP, zolpidem). The second part of the study (days 8 to 14) was an open-label design where all patients who successfully completed days 1 to 7 were eligible to receive open-label treatment with variable-dose Lucemyra™ treatment (as determined by the investigator, but not to exceed 2.88mg total daily dose) in either an inpatient or outpatient setting. No patient received Lucemyra™ for more than 14 days. Two endpoints to support efficacy were the mean Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) total score on days 1 to 7 of treatment and the proportion of patients that completed 7 days of treatment. The SOWS-Gossop, a patient-reported outcome (PRO) instrument, evaluates opioid withdrawal symptoms in which patients are asked to rate their symptom severity as none, mild, moderate, and severe. The SOWS-Gossop total score ranges from 0 to 30 where a higher score indicates a greater withdrawal symptom severity. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on days 1 to 7.
    - The mean SOWS-Gossop scores for days 1 to 7 were 8.8, 6.5, and 6.1 for placebo, Lucemyra™ 2.16mg, and Lucemyra™ 2.88mg, respectively. The mean difference between Lucemyra™ 2.16mg and placebo was -2.3. The mean difference between Lucemyra™ 2.88mg and placebo was -2.7. Both differences were significant. Symptoms assessed on the SOWS-Gossop were recorded as absent or mild for almost all patients remaining to the end of the assessment period.
    - A total of 28% of placebo patients, 41% of Lucemyra™ 2.16mg, and 40% of Lucemyra™ 2.88mg patients completed 7 days of treatment. The difference in proportion in both Lucemyra™ groups was significant compared to placebo. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with Lucemyra™.
- Study 2: Study 2 was an inpatient, randomized, double-blind, placebo-controlled study. Patients were treated with Lucemyra™ [2.88mg/day (0.72mg four times daily)] or matching placebo for 5 days (days 1 to 5). Patients also had access to a variety of support medications for withdrawal symptoms. All patients then received placebo on days 6 and 7 and were discharged on day 8. Two endpoints to support efficacy were the mean SOWS-Gossop total score on days 1 to 5 of treatment and the proportion of patients that completed 5 days of treatment. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on days 1 to 5. A total of 264 patients were

randomized into the study. Of these, 134 patients were randomized to Lucemyra™ 2.88mg/day and 130 patients to placebo.

- The mean SOWS-Gossop scores for days 1 to 5 were 8.9 and 7.0 for placebo and Lucemyra™ 2.88mg, respectively. The mean difference was -1.9 and was statistically significant.
- A total of 33% of placebo patients and 49% of Lucemyra™ patients completed 5 days of treatment. The difference in proportion between the two groups was significant. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with Lucemyra™.

Alpha-2 Adrenergic Agonists: Alpha-2 adrenergic agonists including clonidine (tablets or patches) and Lucemyra™ have been shown to reduce symptoms of opioid withdrawal, particularly autonomic symptoms such as sweating, diarrhea, intestinal cramps, nausea, anxiety, and irritability and have shown comparable efficacy to reducing doses of methadone. Many times alpha-2 adrenergic agonists are used as adjuncts to treatment with buprenorphine or methadone. Contraindications to use of alpha-2 adrenergic agonists include hypotension, moderate or severe renal insufficiency, cardiac instability, pregnancy, and psychosis. Hypotension and sedation may limit use of clonidine or Lucemyra™ for opioid withdrawal, though Lucemyra™ is thought to result in less hypotension than clonidine. A meta-analysis of three clinical trials with a total of 148 opioid dependent patients found that alpha-2 adrenergic agonists were superior to placebo for treatment completion [55% vs. 29%; risk ratio 1.95 (1.34, 2.84)]. Additionally, a meta-analysis of multiple randomized trials found alpha-2 adrenergic agonists to be comparable to reducing doses of methadone in ameliorating opioid withdrawal symptoms in DSM-IV opioid dependent patients. No differences were seen between the treatments in severe withdrawal symptoms [risk ratio 1.18 (0.81, 1.73)], peak withdrawal score, overall withdrawal severity, and rate of treatment completion. The duration of treatment was longer with reducing doses of methadone. Hypotensive and other adverse effects were more likely with alpha-2 adrenergic agonists. Direct comparison research of Lucemyra™ and clonidine does not suggest superior efficacy of one alpha-2 adrenergic agonist in place of the other.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 14 Days
Lucemyra™ (lofexidine) tablets 0.18mg	**$20.69**	**$3,475.92**
clonidine tablets 0.3mg	$0.04	$2.24*
clonidine patches 0.3mg/24 hours	$23.59	$94.36[+]

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
*Dosing based on maximum recommended dosing of 1.2mg/day for 14 days as recommended in the compendia.
[+]Dosing based on dose equivalent to 0.3mg twice daily for 14 days as recommended in the compendia.
Unit = tablet or patch

Sublocade™ (Buprenorphine ER Injection) Product Summary[43]

Indication(s): Sublocade™ (buprenorphine ER injection) is a partial opioid agonist indicated for the treatment of moderate-to-severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

Dosing:

- Sublocade™ is supplied as ER buprenorphine prefilled-syringes intended for sub-Q injection in the following strengths: 100mg/0.5mL and 300mg/1.5mL.
- Under the Drug Addiction Treatment Act (DATA), prescription use of Sublocade™ in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe Sublocade™ for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.
- Sublocade™ is distributed through a restricted distribution system, which is intended to prevent the direct distribution to a patient. Sublocade™ should only be dispensed directly to a healthcare provider for administration by a healthcare provider.
- Initiating treatment with Sublocade™ as the first buprenorphine product has not been studied. Sublocade™ treatment should only be initiated following induction and dose-adjustment with a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24mg of buprenorphine daily for a minimum of 7 days.
- Sublocade™ is administered monthly by sub-Q injection in the abdominal region.
- The recommended dose of Sublocade™ is two monthly initial doses of 300mg followed by 100mg monthly maintenance doses. Increasing the maintenance dose to 300mg monthly may be considered for patients who tolerate the 100mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.
- A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.
- Sublocade™ is injected as a liquid, and the subsequent precipitation of the poly (DL-lactide-co-glycolide) polymer creates a solid depot which contains buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot. Clinical monitoring for evidence at the injection site of tampering or attempting to remove the depot should be ongoing throughout treatment. No accounts of subjects removing or attempting to remove the depot after administration of Sublocade™ were reported in premarketing studies.
- Due to the chronic nature of opioid use disorder, the need for continuing MAT should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment.

Boxed Warning: Risk of serious harm or death with IV administration; Sublocade™ Risk Evaluation and Mitigation Strategy (REMS)

Efficacy: The efficacy of Sublocade™ was established in a Phase 3 double-blind efficacy and safety study and an opioid blockade study.

- <u>Opioid Blockade Study:</u> The opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics, and safety of sub-Q Sublocade™ in 39 subjects with opioid use disorder. The Emax effect of “drug liking” on a VAS measurement after challenge with intramuscular (IM) injections of 6mg and 18mg hydromorphone was not

inferior (i.e., shown to be not substantially more likeable) compared to the Emax of "drug liking" on a VAS, measured after challenge with placebo (at weeks 1 through 4 following the first injection of 300mg Sublocade™). All 12 weeks of the treatment period demonstrated blockade for both 6mg and 18mg hydromorphone following Sublocade™ injections. For comparison, stabilization doses of SL buprenorphine in week 0 failed to provide full blockade to 18mg of hydromorphone.

- Phase 3 Efficacy Study: The efficacy of Sublocade™ for the treatment of opioid use disorder was evaluated in a Phase 3, 24-week, randomized, double-blind, placebo-controlled trial in treatment-seeking patients who met the DSM-5 criteria for moderate or severe opioid use disorder. Patients were randomized to one of following dosing regimens: six once-monthly 300mg doses, 2 once-monthly 300mg doses followed by four once-monthly 100mg doses, or 6 once-monthly sub-Q injections of placebo. Prior to the first dose, treatment was initiated with buprenorphine/naloxone SL film over a period of 7 to 14 days. After randomization, supplemental dosing with buprenorphine/naloxone SL film was not permitted during the study. Efficacy was evaluated over weeks 5 through 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A "grace period" was applied for weeks 1 through 4 to allow patients to stabilize on treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during weeks 5 to 24 were counted as positive for illicit opioids. A total of 504 patients were randomized (203 subjects in the 300mg/100mg group, 201 patients in the 300mg/300mg group, and 100 patients in the placebo group).
    - Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use, regardless of dose, Sublocade™ was superior to the placebo group with statistical significance. The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in both groups receiving Sublocade™ compared to the placebo group (300mg/100mg: 28.4%, 300mg/300mg: 29.1%, placebo: 2%).

Cost Comparison:

Medication	Cost Per Month	Cost Per Year
Sublocade™ (buprenorphine ER injection) 100mg/0.5mL	**$1,580.00**	**$18,960.00⁺**
Sublocade™ (buprenorphine ER injection) 300mg/1.5mL	**$1,580.00**	**$18,960.00⁺**
Suboxone® (buprenorphine/naloxone SL film) 8mg/2mg	$704.70	$8,456.40*^
buprenorphine/naloxone SL tablets 8mg/2mg	$221.40	$2,656.80^

SL= sublingual; ER = extended-release

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

⁺Costs based on maintenance dosing after initial dosing established. Cost per year based on dosing every 30 days or 12 monthly doses.

*Supplementally rebated product.

^Dosing based on maximum recommended dose of 24mg of buprenorphine per day.

Recommendations

The College of Pharmacy recommends the following:

1. The placement of Apadaz® (benzhydrocodone/APAP) into Tier-3 of the Opioid Analgesics Product Based Prior Authorization (PBPA) category. Current short-acting Tier-3 criteria will apply.
2. The prior authorization of Lucemyra™ (lofexidine) and Sublocade™ (buprenorphine ER injection) with the following criteria:

Lucemyra™ (Lofexidine) Approval Criteria:

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

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

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

Utilization Details of Opioid Analgesics: Calendar Year 2017

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	67,598	13,173	$1,511,097.67	5.13	$22.35
HYDROCO/APAP TAB 7.5-325MG	56,442	27,354	$992,889.31	2.06	$17.59
HYDROCO/APAP TAB 5-325MG	38,533	26,465	$514,543.90	1.46	$13.35
HYDROCO/APAP SOL 7.5-325MG	8,406	7,742	$230,201.81	1.09	$27.39
HYDROCOD/IBU TAB 7.5-200MG	1,101	445	$28,887.10	2.47	$26.24
LORCET HD TAB 10-325MG	429	166	$10,164.25	2.58	$23.69
HYDROCOD/IBU TAB 10-200MG	173	28	$41,505.49	6.18	$239.92
IBUDONE TAB 10-200MG	41	12	$4,925.86	3.42	$120.14
LORCET TAB 5-325MG	36	31	$462.65	1.16	$12.85
HYDROCO/APAP TAB 2.5-325MG	17	6	$957.57	2.83	$56.33
HYDROCOD/IBU TAB 5-200MG	16	11	$1,876.93	1.45	$117.31
LORCET PLUS TAB 7.5-325MG	12	12	$220.19	1	$18.35
IBUDONE TAB 5-200MG	6	4	$476.52	1.5	$79.42
SUBTOTAL	**172,810**	**65,221**	**$3,338,209.25**	**2.65**	**$19.32**
IMMEDIATE-RELEASE OXYCODONE PRODUCTS					
OXYCOD/APAP TAB 10-325MG	23,732	5,410	$1,099,964.38	4.39	$46.35
OXYCOD/APAP TAB 5-325MG	18,423	14,664	$248,013.19	1.26	$13.46
OXYCOD/APAP TAB 7.5-325MG	11,573	5,159	$355,565.75	2.24	$30.72
OXYCODONE TAB 15MG	7,460	1,362	$193,260.89	5.48	$25.91
OXYCODONE TAB 30MG	5,844	938	$227,606.22	6.23	$38.95
OXYCODONE TAB 10MG	5,771	1,482	$131,798.71	3.89	$22.84
OXYCODONE TAB 20MG	3,888	676	$147,897.14	5.75	$38.04
OXYCODONE TAB 5MG	2,557	1,389	$38,198.14	1.84	$14.94
OXYCODONE SOL 5MG/5ML	357	288	$14,139.97	1.24	$39.61
ENDOCET TAB 10-325MG	325	101	$16,998.60	3.22	$52.30
OXYCODONE CAP 5MG	56	41	$3,455.94	1.37	$61.71
ENDOCET TAB 5-325MG	36	34	$516.41	1.06	$14.34
OXYCOD/APAP TAB 2.5-325MG	32	8	$3,655.06	4	$114.22
ENDOCET TAB 7.5-325MG	31	17	$1,116.28	1.82	$36.01
OXYCOD/ASA TAB 4.8355-325MG	31	29	$826.94	1.07	$26.68
OXYCODONE CON 100MG/5ML	19	8	$13,375.52	2.38	$703.97
OXYCODONE CON 20MG/ML	9	6	$3,959.08	1.5	$439.90
OXYCODONE POW HCL	1	1	$6.70	1	$6.70
OXAYDO TAB 7.5MG	1	1	$557.15	1	$557.15
SUBTOTAL	**80,146**	**26,931**	**$2,500,912.07**	**2.98**	**$31.20**
CODEINE PRODUCTS					
APAP/CODEINE TAB 300-30MG	19,248	13,629	$256,080.90	1.41	$13.30
APAP/CODEINE TAB 300-60MG	8,872	2,824	$232,058.33	3.14	$26.16
APAP/CODEINE SOL 120-12MG/5ML	4,546	4,208	$52,090.93	1.08	$11.46
BUT/APAP/CAF/COD CAP 50-325-40-30MG	773	276	$51,629.52	2.8	$66.79
BUT/ASA/CAF/COD CAP 50-325-40-30MG	271	73	$33,065.51	3.71	$122.01
ASCOMP/COD CAP 50-325-40-30MG	103	46	$8,856.62	2.24	$85.99
APAP/CODEINE TAB 300-15MG	68	64	$810.98	1.06	$11.93
CODEINE SULF TAB 60MG	15	4	$1,051.56	3.75	$70.10
CODEINE SULF TAB 30MG	5	2	$317.10	2.5	$63.42

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
CODEINE SULF TAB 15MG	3	3	$69.53	1	$23.18
DIHYDROCOD/ASA/CAFF CAP 356.4-30-16MG	1	1	$99.42	1	$99.42
SUBTOTAL	**33,905**	**20,328**	**$636,130.40**	**1.67**	**$18.76**
IMMEDIATE-RELEASE HYDROMORPHONE PRODUCTS					
HYDROMORPHON TAB 4MG	1,188	306	$20,914.14	3.88	$17.60
HYDROMORPHON TAB 2MG	655	385	$8,710.21	1.7	$13.30
HYDROMORPHON TAB 8MG	430	83	$17,079.15	5.18	$39.72
HYDROMORPHON LIQ 1MG/ML	13	8	$990.76	1.63	$76.21
DILAUDID TAB 8MG	9	1	$6,382.33	9	$709.15
HYDROMORPHON INJ 500MG/50ML	3	2	$944.17	1.5	$314.72
HYDROMORPHON POW HCL	2	1	$198.79	2	$99.40
HYDROMORPHON INJ 4MG/ML	2	1	$25.80	2	$12.90
HYDROMORPHON INJ 10MG/ML	1	1	$45.45	1	$45.45
HYDROMORPHON INJ 50MG/5ML	1	1	$45.83	1	$45.83
SUBTOTAL	**2,304**	**737**	**$55,336.63**	**3.13**	**$24.02**
IMMEDIATE-RELEASE MORPHINE PRODUCTS					
MORPHINE SUL TAB 15MG	2,246	543	$51,900.37	4.14	$23.11
MORPHINE SUL TAB 30MG	744	142	$21,062.54	5.24	$28.31
MORPHINE SUL SOL 100MG/5ML	108	62	$6,621.71	1.74	$61.31
MORPHINE SUL SOL 10MG/5ML	71	39	$1,280.85	1.82	$18.04
MORPHINE SUL SOL 20MG/5ML	14	7	$643.57	2	$45.97
MORPHINE SUL INJ 50MG/ML	1	1	$70.74	1	$70.74
SUBTOTAL	**3,184**	**741**	**$81,579.78**	**4.3**	**$25.62**
IMMEDIATE-RELEASE TRAMADOL PRODUCTS					
TRAMADOL HCL TAB 50MG	41,458	16,152	$411,843.88	2.57	$9.93
TRAMADOL/APAP TAB 37.5-325MG	583	424	$9,546.05	1.38	$16.37
SUBTOTAL	**42,041**	**16,492**	**$421,389.93**	**2.55**	**$10.02**
IMMEDIATE-RELEASE TAPENTADOL PRODUCTS					
NUCYNTA TAB 50MG	74	25	$35,679.25	2.96	$482.15
NUCYNTA TAB 100MG	36	8	$18,880.96	4.5	$524.47
NUCYNTA TAB 75MG	18	4	$11,807.63	4.5	$655.98
SUBTOTAL	**128**	**33**	**$66,367.84**	**3.88**	**$518.50**
IMMEDIATE-RELEASE OXYMORPHONE PRODUCTS					
OXYMORPHONE TAB HCL 10MG	331	46	$60,498.51	7.2	$182.77
OXYMORPHONE TAB HCL 5MG	77	17	$9,059.49	4.53	$117.66
SUBTOTAL	**408**	**62**	**$69,558.00**	**6.58**	**$170.49**
IMMEDIATE-RELEASE FENTANYL PRODUCTS					
SUBSYS SPR 200MCG	13	4	$59,157.80	3.25	$4,550.60
FENTANYL CIT INJ 100MCG	8	7	$94.16	1.14	$11.77
SUBSYS SPR 100MCG	3	2	$6,683.68	1.5	$2,227.89
FENTANYL CIT INJ 2500MCG	1	1	$63.98	1	$63.98
SUBTOTAL	**25**	**12**	**$65,999.62**	**2.08**	**$2,639.98**
PENTAZOCINE PRODUCTS					
PENTAZ/NALOX TAB 50-0.5MG	819	371	$120,537.11	2.21	$147.18
SUBTOTAL	**819**	**371**	**$120,537.11**	**2.21**	**$147.18**
MEPERIDINE PRODUCTS					
MEPERIDINE TAB 50MG	531	345	$14,878.11	1.54	$28.02
MEPERIDINE SOL 50MG/5ML	462	347	$4,504.50	1.33	$9.75
MEPERIDINE TAB 100MG	45	8	$2,209.60	5.63	$49.10
MEPERIDINE INJ 100MG/ML	2	2	$15.82	1	$7.91

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBTOTAL	**1,040**	**701**	**$21,608.03**	**1.48**	**$20.78**
TOTAL	**336,810**	**105,415***	**$7,337,628.66**	**3.20**	**$21.90**

*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	751	189	$335,234.82	3.97	$446.38
HYSINGLA ER TAB 20MG	629	196	$144,684.58	3.21	$230.02
HYSINGLA ER TAB 30MG	581	168	$192,728.79	3.46	$331.72
HYSINGLA ER TAB 60MG	261	74	$158,492.32	3.53	$607.25
HYSINGLA ER TAB 80MG	185	27	$152,708.39	6.85	$825.45
HYSINGLA ER TAB 120MG	38	3	$44,557.07	12.67	$1,172.55
HYSINGLA ER TAB 100MG	38	9	$42,167.35	4.22	$1,109.67
ZOHYDRO ER CAP 30MG	4	2	$2,094.32	2	$523.58
ZOHYDRO ER CAP 20MG	2	1	$985.71	2	$492.86
ZOHYDRO ER CAP 40MG	1	1	$542.09	1	$542.09
ZOHYDRO ER CAP 15MG	1	1	$497.98	1	$497.98
ZOHYDRO ER CAP 10MG	1	1	$467.28	1	$467.28
SUBTOTAL	**2,492**	**529**	**$1,075,160.70**	**4.71**	**$431.44**
EXTENDED-RELEASE OXYCODONE PRODUCTS					
OXYCONTIN TAB 20MG CR	3,246	664	$1,116,038.53	4.89	$343.82
OXYCONTIN TAB 10MG CR	1,927	521	$348,531.29	3.7	$180.87
OXYCONTIN TAB 30MG CR	1,641	326	$811,570.60	5.03	$494.56
OXYCONTIN TAB 40MG CR	1,477	273	$904,829.20	5.41	$612.61
OXYCONTIN TAB 15MG CR	1,373	313	$381,733.49	4.39	$278.03
OXYCONTIN TAB 80MG CR	907	128	$1,164,857.30	7.09	$1,284.30
OXYCONTIN TAB 60MG CR	872	143	$781,529.11	6.1	$896.25
OXYCODONE TAB 40MG ER	44	13	$16,278.29	3.38	$369.96
OXYCODONE TAB 80MG ER	14	9	$10,473.43	1.56	$748.10
XTAMPZA ER CAP 18MG	3	2	$1,212.07	1.5	$404.02
XTAMPZA ER CAP 36MG	2	1	$826.89	2	$413.45
XTAMPZA ER CAP 13.5MG	2	1	$672.84	2	$336.42
XTAMPZA ER CAP 27MG	1	1	$563.31	1	$563.31
OXYCODONE TAB 20MG ER	1	1	$234.25	1	$234.25
XTAMPZA ER CAP 9MG	1	1	$215.25	1	$215.25
OXYCODONE TAB 10MG ER	1	1	$148.18	1	$148.18
SUBTOTAL	**11,512**	**1,815**	**$5,539,714.03**	**6.34**	**$481.21**
EXTENDED-RELEASE HYDROMORPHONE PRODUCTS					
HYDROMORPHONE TAB 32MG ER	27	5	$65,263.80	5.4	$2,417.18
HYDROMORPHONE TAB 12MG ER	18	5	$10,639.34	3.6	$591.07
HYDROMORPHONE TAB 16MG ER	18	7	$8,941.70	2.57	$496.76
HYDROMORPHONE TAB 8MG ER	17	5	$4,569.89	3.4	$268.82
EXALGO TAB 32MG	12	2	$19,967.98	6	$1,664.00
EXALGO TAB 12MG	2	1	$2,273.19	2	$1,136.60
SUBTOTAL	**94**	**18**	**$111,655.90**	**5.22**	**$1,187.83**
EXTENDED-RELEASE MORPHINE PRODUCTS					

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
MORPHINE SUL TAB 30MG ER	4,185	704	$166,032.43	5.94	$39.67
MORPHINE SUL TAB 15MG ER	4,150	835	$107,388.76	4.97	$25.88
MORPHINE SUL TAB 60MG ER	1,760	255	$115,704.92	6.9	$65.74
MORPHINE SUL TAB 100MG ER	480	74	$51,982.32	6.49	$108.30
EMBEDA CAP 30-1.2MG	53	10	$18,553.81	5.3	$350.07
MORPHINE SUL TAB 200MG ER	53	7	$12,724.69	7.57	$240.09
MORPHINE SUL CAP 30MG ER	50	11	$8,777.91	4.55	$175.56
EMBEDA CAP 20-0.8MG	47	17	$11,057.95	2.76	$235.28
MORPHINE SUL CAP 90MG ER	22	3	$8,981.60	7.33	$408.25
MORPHINE SUL CAP 50MG ER	21	4	$4,572.27	5.25	$217.73
MORPHINE SUL CAP 60MG ER	20	4	$7,802.81	5	$390.14
MORPHINE SUL CAP 20MG ER	16	9	$2,816.10	1.78	$176.01
KADIAN CAP 50MG ER	13	1	$12,875.50	13	$990.42
KADIAN CAP 200MG ER	12	1	$51,747.60	12	$4,312.30
MORPHINE SUL CAP 80MG ER	10	2	$5,116.52	5	$511.65
MS CONTIN TAB 60MG ER	8	1	$30,826.02	8	$3,853.25
MORPHINE SUL CAP 10MG ER	8	2	$1,195.09	4	$149.39
KADIAN CAP 40MG ER	6	2	$1,957.61	3	$326.27
MORPHABOND TAB 30MG ER	2	1	$1,309.10	2	$654.55
MORPHINE SUL CAP 100MG ER	2	1	$1,151.84	2	$575.92
MORPHABOND TAB 15MG ER	1	1	$330.55	1	$330.55
MORPHINE SUL CAP 30MG ER	1	1	$281.57	1	$281.57
SUBTOTAL	**10,920**	**1,625**	**$623,186.97**	**6.72**	**$57.07**
EXTENDED-RELEASE TRAMADOL PRODUCTS					
TRAMADOL HCL TAB 200MG ER	8	2	$685.71	4	$85.71
TRAMADOL HCL TAB 100MG ER	3	2	$199.46	1.5	$66.49
TRAMADOL HCL TAB 300MG ER	1	1	$116.49	1	$116.49
SUBTOTAL	**12**	**5**	**$1,001.66**	**2.4**	**$83.47**
EXTENDED-RELEASE TAPENTADOL PRODUCTS					
NUCYNTA ER TAB 100MG	54	8	$30,625.97	6.75	$567.15
NUCYNTA ER TAB 250MG	32	4	$39,198.30	8	$1,224.95
NUCYNTA ER TAB 50MG	32	14	$10,500.21	2.29	$328.13
NUCYNTA ER TAB 200MG	19	3	$17,394.97	6.33	$915.52
NUCYNTA ER TAB 150MG	17	5	$12,822.60	3.4	$754.27
SUBTOTAL	**154**	**29**	**$110,542.05**	**5.31**	**$717.81**
EXTENDED-RELEASE OXYMORPHONE PRODUCTS					
OPANA ER TAB 10MG	89	19	$24,534.77	4.68	$275.67
OPANA ER TAB 30MG	76	12	$50,730.01	6.33	$667.50
OPANA ER TAB 20MG	76	15	$38,470.04	5.07	$506.18
OPANA ER TAB 40MG	63	10	$86,633.49	6.3	$1,375.13
OPANA ER TAB 15MG	35	8	$13,780.87	4.38	$393.74
OXYMORPHONE TAB 40MG ER	7	2	$5,178.26	3.5	$739.75
OXYMORPHONE TAB 20MG ER	4	1	$1,268.56	4	$317.14
OPANA ER TAB 7.5MG	2	1	$456.38	2	$228.19
OXYMORPHONE TAB 10MG ER	1	1	$167.96	1	$167.96
OPANA ER TAB 5MG	1	1	$76.85	1	$76.85
SUBTOTAL	**354**	**56**	**$221,297.19**	**6.32**	**$625.13**
EXTENDED-RELEASE FENTANYL PRODUCTS					
FENTANYL DIS 25MCG/HR	1,533	383	$64,622.59	4	$42.15
FENTANYL DIS 50MCG/HR	1,429	311	$90,403.25	4.59	$63.26

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
FENTANYL DIS 75MCG/HR	990	182	$91,631.52	5.44	$92.56
FENTANYL DIS 100MCG/HR	783	150	$89,295.30	5.22	$114.04
FENTANYL DIS 12MCG/HR	555	176	$66,577.33	3.15	$119.96
FENTANYL DIS 37.5MCG/HR	108	25	$48,928.07	4.32	$453.04
DURAGESIC DIS 50MCG/HR	13	1	$8,744.63	13	$672.66
SUBTOTAL	**5,411**	**889**	**$460,202.69**	**6.09**	**$85.05**
METHADONE PRODUCTS					
METHADONE TAB 10MG	1,490	172	$34,152.44	8.66	$22.92
METHADONE TAB 5MG	114	22	$2,475.60	5.18	$21.72
METHADONE SOL 5MG/5ML	25	23	$234.35	1.09	$9.37
METHADONE SOL 10MG/5ML	3	1	$83.61	3	$27.87
METHADOSE CON 10MG/ML	1	1	$10.55	1	$10.55
SUBTOTAL	**1,633**	**210**	**$36,956.55**	**7.78**	**$22.63**
BUPRENORPHINE PAIN PRODUCTS					
BUTRANS DIS 10MCG/HR	616	274	$221,998.31	2.25	$360.39
BUTRANS DIS 15MCG/HR	435	144	$224,279.23	3.02	$515.58
BUTRANS DIS 20MCG/HR	291	80	$183,672.89	3.64	$631.18
BUTRANS DIS 5MCG/HR	181	98	$43,894.24	1.85	$242.51
BUPRENORPHIN DIS 10MCG/HR	132	75	$38,426.05	1.76	$291.11
BUTRANS DIS 7.5MCG/HR	123	45	$41,512.29	2.73	$337.50
BUPRENORPHIN DIS 15MCG/HR	67	39	$28,033.72	1.72	$418.41
BELBUCA MIS 300MCG	66	27	$28,078.02	2.44	$425.42
BUPRENORPHIN DIS 20MCG/HR	55	25	$30,624.67	2.2	$556.81
BELBUCA MIS 150MCG	41	24	$11,329.41	1.71	$276.33
BUPRENORPHIN DIS 5MCG/HR	39	23	$7,834.40	1.7	$200.88
BELBUCA MIS 75MCG	28	19	$7,090.64	1.47	$253.24
BUPRENORPHIN DIS 7.5MCG/HR	27	16	$7,347.81	1.69	$272.14
BELBUCA MIS 450MCG	14	8	$8,075.14	1.75	$576.80
BELBUCA MIS 750MCG	12	2	$8,076.48	6	$673.04
BELBUCA MIS 600MCG	7	4	$4,357.37	1.75	$622.48
SUBTOTAL	**2,134**	**621**	**$894,630.67**	**3.44**	**$419.23**
TOTAL	**34,716**	**5,086***	**$9,074,348.41**	**6.83**	**$261.39**

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

Utilization Details of MAT Medications: Calendar Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBOXONE MIS 8-2MG	8,110	1,117	$3,562,211.13	7.26	$439.24
NALTREXONE TAB 50MG	2,871	590	$117,030.82	4.87	$40.76
BUPREN/NALOX SUB 8-2MG	2,596	444	$562,458.44	5.85	$216.66
BUPRENORPHIN SUB 8MG	1,472	248	$143,689.82	5.94	$97.62
SUBOXONE MIS 4-1MG	133	26	$40,824.77	5.12	$306.95
ZUBSOLV SUB 5.7-1.4MG	132	24	$70,192.62	5.5	$531.76
SUBOXONE MIS 2-0.5MG	132	40	$24,654.93	3.3	$186.78
BUPREN/NALOX SUB 2-0.5MG	95	23	$12,322.27	4.13	$129.71
BUPRENORPHIN SUB 2MG	80	25	$3,789.12	3.2	$47.36
VIVITROL INJ 380MG	80	27	$110,503.04	2.96	$1,381.29
SUBOXONE MIS 12-3MG	56	11	$41,927.80	5.09	$748.71

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
BUNAVAIL MIS 4.2-0.7MG	19	9	$7,102.77	2.11	$373.83
ZUBSOLV SUB 8.6-2.1MG	17	5	$10,576.08	3.4	$622.12
BUNAVAIL MIS 2.1-0.3MG	6	1	$1,561.79	6	$260.30
ZUBSOLV SUB 2.9-0.71MG	3	1	$711.72	3	$237.24
BUNAVAIL MIS 6.3-1MG	3	3	$1,108.37	1	$369.46
TOTAL	**15,805**	**2,196***	**$4,710,665.49**	**7.2**	**$298.05**

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

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Appendix K

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

Oklahoma Health Care Authority
July 2018

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

Autosomal dominant polycystic kidney disease (ADPKD) is a progressively debilitating genetic disorder in which fluid-filled cysts develop in the kidneys over time. The cysts enlarge the kidneys and impair their ability to function normally, leading to kidney failure in most patients. ADPKD is the most common genetic cause of chronic kidney disease (CKD) occurring in all races, with an estimated prevalence of 140,000 people in the United States, and is the underlying cause of approximately 5% of patients who initiate hemodialysis in the United States. ADPKD is caused by two known (and possibly more unknown) genetic mutations: *PKD1* (encodes polycystin-1) on chromosome 16 and *PKD2* (encodes polycystin-2) on chromosome 4. *PKD1* mutations are the most common (estimated up to 85%), the most severe phenotype, and have an earlier-onset than *PKD2* [end-stage renal disease (ESRD) mean age 54.3 years vs. 74.0 years in *PKD1* versus *PKD2*].

The diagnosis of ADPKD is based on imaging of the kidneys; typical findings include large kidneys and extensive cysts scattered throughout both kidneys. Screening in children less than 18 years of age is not recommended since adverse effects from a pre-symptomatic diagnosis outweigh current benefits. Patients with ADPKD can present with hypertension, proteinuria, renal insufficiency, and flank pain due to renal hemorrhage, calculi, or urinary tract infection. The major extrarenal manifestations can include hepatic and pancreatic cysts, cerebral aneurysms, cardiac valve disease, colonic diverticula, abdominal wall and inguinal hernia, and seminal vesical cysts. The age at which individuals have clinical manifestations such as renal failure or hypertension is variable, and patients with *PKD1* present with symptoms at a younger age than *PKD2*. The diagnosis is most commonly made in the setting of routine screening in an asymptomatic patient with a positive family history of ADPKD, during initial work-up for new-onset hypertension, as an accidental finding during an imaging study performed for an unrelated reason (e.g., trauma, pregnancy), or during evaluation of ADPKD-specific symptoms (e.g., hematuria, cyst rupture, kidney stones).

In most patients, renal function remains intact until the fourth decade of life. Once the glomerular filtration rate (GFR) starts to decline, the average GFR reduction ranges from 4.4 to 5.9mL/min decline per year. Patients who present with symptoms at an early age are more likely to develop ESRD. In one study, patients diagnosed before 30 years of age had a mean survival that was 10 years or less than those diagnosed after age 30. Most patients with ADPKD die from cardiac causes, particularly myocardial infarction (MI) or congestive heart failure (CHF).

The treatment of ADPKD patients include nonspecific measures such as strict blood pressure control, dietary protein restriction, a low-sodium diet, and statins, which may prevent progression of disease and reduce cardiovascular mortality. Hypertension occurs early, prior to the loss of kidney function, in about two-thirds of ADPKD patients and is associated with progressive renal disease. Rigorous control of blood pressure may prevent progression of renal disease and decrease the risk of cardiovascular morbidity that characterizes all patients with CKD. Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may, in addition to lowering blood pressure, slow the rate of progression of ADPKD. Patients with ADPKD and renal failure are commonly treated with hemodialysis or undergo renal transplantation with equivalent or better overall outcomes compared with non-ADPKD patients.

On April 24, 2018, Jynarque™ (tolvaptan), the first treatment for ADPKD, was approved by the U.S. Food and Drug Administration (FDA). Jynarque™ is a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD. Jynarque™ is available as oral tablets in five strengths: 15mg, 30mg, 45mg, 60mg, and 90mg. Due to the risk of serious liver injury, Jynarque™ is only available through a restricted distribution program called Jynarque™ Risk Evaluation Mitigation Strategy (REMS) program. Tolvaptan is also commercially available as Samsca® 15mg and 30mg oral tablets which was approved by the FDA in May of 2009 for the treatment of patients with clinically significant hypervolemic or euvolemic hyponatremia (serum sodium <125mEq/L or less-marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Samsca® should only be initiated and re-initiated in a hospital where serum sodium can be monitored closely. Jynarque™ may be initiated outpatient and abnormalities in sodium concentrations must be corrected prior to initiation of therapy. Due to the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS program for Jynarque™.

Market News and Updates[10,11,12]

New FDA Approval(s):

- **April 2018:** The FDA approved Jynarque™ (tolvaptan), a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

News:

- **October 2017:** Palladio Biosciences received Orphan Drug designation from the FDA for lixivaptan, a potent, selective vasopressin V_2-receptor antagonist, for the treatment of ADPKD. Palladio Biosciences states that it recognized the need for a drug with a similar mechanism of action to tolvaptan but without its liver toxicity risks. Lixivaptan was previously administered to 1,673 subjects across 36 clinical studies as part of a prior clinical development program for the treatment of hyponatremia. Palladio expects to leverage lixivaptan's large body of data generated in the hyponatremia clinical program to repurpose lixivaptan and advance its development for the treatment of ADPKD.

Lixivaptan has shown no evidence of liver toxicity in the clinical studies conducted so far. In April 2018, the FDA granted Investigational New Drug (IND) clearance for the ELISA (Evaluation of Lixivaptan In Subjects with ADPKD) Study, a Phase 2 clinical trial that will evaluate the safety, pharmacokinetics, and pharmacodynamics of multiple doses of lixivaptan in patients with ADPKD with relatively preserved kidney function (CKD stages 1 and 2) and moderately impaired renal function (CKD stage 3). The study is expected to enroll 32 patients beginning the end of June 2018.

Jynarque™ (Tolvaptan) Product Summary[7,13,14]

Indication(s): Jynarque™ (tolvaptan) is a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

Dosing:

- Jynarque™ (tolvaptan) is available as oral tablets in five strengths: 15mg, 30mg, 45mg, 60mg, and 90mg. Jynarque™ will be packaged in 7-day blister cards (14 tablets per card) and as 28-day cartons (4 blister cards per carton) containing 45mg/15mg, 60mg/30mg, or 90mg/30mg tablets per pack.
- The initial recommended dose of Jynarque™ is 60mg per day taken as 45mg upon waking and 15mg 8 hours later. The dose should be titrated to 60mg plus 30mg then 90mg plus 30mg per day if tolerated with at least weekly intervals between titrations.
- Patients may down-titrate based on tolerability.
- Patients should drink enough water to avoid thirst or dehydration.
- Dose adjustment is recommended for patients taking moderate CYP3A inhibitors.

Boxed Warning: Risk of Serious Liver Injury

- Jynarque™ (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported.
- Transaminases and bilirubin should be measured before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months, and every 3 months thereafter.
- Jynarque™ is available only through a restricted distribution program called the Jynarque™ REMS Program.

Mechanism of Action: Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V_2-receptor is 29 times that for the V_{1a}-receptor. Decreased binding of vasopressin to the V_2-receptor in the kidney lowers adenylate cyclase activity resulting in a decrease in intracellular adenosine 3', 5'-cyclic monophosphate (cAMP) concentrations. Decreased cAMP concentrations prevent aquaporin-2 containing vesicles from fusing with the plasma membrane, which in turn causes an increase in urine water excretion, an increase in free water clearance (aquaresis), and a decrease in urine osmolality. In human ADPKD cyst epithelial cells, tolvaptan inhibited AVP-stimulated *in vitro* cyst growth and chloride-dependent fluid secretion into cysts. In animal models, decreased cAMP concentrations were associated with decreases in the rate of growth of total kidney volume (TKV) and the rate of formation and

enlargement of kidney cysts. Tolvaptan metabolites have no or weak antagonist activity for human V_2-receptors compared with tolvaptan.

Contraindication(s):

- History of signs or symptoms of significant liver impairment or injury that does not include uncomplicated polycystic liver disease
- Concomitant use of strong CYP3A inhibitors
- Uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity to tolvaptan or any of its components
- Uncorrected urinary outflow obstruction
- Anuria

Safety:

- Hypernatremia, Dehydration, and Hypovolemia: Jynarque™ increases free water clearance and, as a result, may cause dehydration, hypovolemia, and hypernatremia. Therefore, abnormalities in sodium concentrations should be corrected prior to initiation of therapy. Patients should drink water when thirsty, and throughout the day and night, if awake. Signals of dehydration (e.g., weight loss, tachycardia, hypotension) should be monitored and intervention may be required.

Use in Specific Populations:

- Pregnancy: Jynarque™ may cause fetal harm. Available data with Jynarque™ use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes.
- Lactation: Breastfeeding is not recommended during treatment with Jynarque™. There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion in breastfed infants, women should be advised not to breastfeed during treatment with Jynarque™.
- Pediatric Use: The safety and effectiveness of Jynarque™ in pediatric patients have not been established.
- Geriatric Use: Clinical studies of Jynarque™ did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 concomitant disease(s) or other drug therapies.
- Hepatic Impairment: Use of Jynarque™ is contraindicated in patients with a history of or signs or symptoms of significant liver impairment or injury.

- Renal Impairment: Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60mL/min, while REPRISE included patients with an estimated glomerular filtration rate (eGFR) of 25 to 65mL/min/1.73m^2.

Drug Interactions:

- Strong CYP3A Inducers: Co-administration of Jynarque™ with strong CYP3A inducers reduces exposure to Jynarque™. Concomitant use of Jynarque™ with strong CYP3A inducers should be avoided.
- CYP3A Inhibitors: Larger doses of the strong CYP3A inhibitor ketoconazole would be expected to produce larger increases in tolvaptan exposure. Concomitant use of Jynarque™ with strong CYP3A inhibitors is contraindicated. Dose reduction of Jynarque™ is recommended for patients while taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking Jynarque™.
- OATP1B1/3 and OAT3 Transporter Substrates: The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/3 and OAT3 *in vitro*. Patients who take Jynarque™ should avoid concomitant use with OATP1B1/3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- Breast Cancer Resistance Protein (BCRP) Transporter Substrates: Tolvaptan is an inhibitor of BCRP. Patients who take Jynarque™ should avoid concomitant use with BCRP substrates (e.g., rosuvastatin).
- V_2-Receptor Agonists: As a V_2-receptor antagonist, tolvaptan will interfere with the V_2-agonist activity of desmopressin (DDAVP®). Concomitant use of Jynarque™ with a V_2-agonist should be avoided.

Adverse Reactions: The most common adverse reactions observed with Jynarque™ (incidence >10% and at least twice that for placebo) in clinical studies were thirst, polyuria, nocturia, pollakiuria, and polydipsia.

Efficacy: Jynarque™ was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages of disease.

TEMPO 3:4: Trial in Early, Rapidly-Progressing ADPKD:

- TEMPO 3:4 enrolled 1,445 patients 18 years of age and older with earlier [estimated creatinine clearance (eCrCl) ≥60mL/min], rapidly-progressing (TKV ≥750mL and age <51 years) ADPKD randomized 2:1 to treatment with Jynarque™ or placebo for up to 3 years.
- The primary endpoint was the annual rate of change of TKV. Over a 3-year period, the increase in TKV in the Jynarque™ group was 2.8% per year [95% confidence interval (CI): 2.5 to 3.1], versus 5.5% per year in the placebo group (95% CI: 5.1 to 6.0; P<0.001). The difference in TKV between treatment groups mostly developed within the first year, the earliest assessment, with little further difference in years two and three. In years four and five during the TEMPO 3:4 extension trial, both groups received Jynarque™ and the difference between the groups in TKV was not maintained. Jynarque™ has little effect on kidney size beyond what accrues during the first year of treatment.

- The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression of the following events: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category). The relative rate of ADPKD-related events decreased by 13.5% in Jynarque™-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio: 0.87; 95% CI: 0.78 to 0.97; P=0.0095).
- The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0mL/min/1.73m^2/year (95% CI: 0.6, 1.4). In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of Jynarque™ treatment.

<u>REPRISE: Trial in Later-Stage ADPKD:</u>

- REPRISE enrolled 1,519 patients 18 to 65 years of age with CKD with an eGFR between 25 and 65mL/min/1.73m^2 if younger than 56 years of age or with an eGFR between 25 and 44mL/min/1.73m^2 plus eGFR decline >2.0 mL/min/1.73m^2/year if between 56 and 65 years of age.
- Patients were treated for 12 months followed by a 3-week follow-up period to assess renal function after completion of treatment. Prior to randomization, patients were required to complete sequential, single-blind run-in periods during which they received placebo for 1 week, followed by Jynarque™ titration for 2 weeks, and then treatment with Jynarque™ at the highest tolerated dose achieved during titration for 3 weeks. Only patients who could tolerate the two highest doses of Jynarque™ (60mg/30mg or 90mg/30mg) for the subsequent 3 weeks were randomized 1:1 to treatment with Jynarque™ or placebo.
- Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease, and/or increase as clinical circumstances warranted, within the range of titrated doses.
- Of the total 1,519 patients enrolled in the study, 1,370 successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1,313 subjects were included in the primary efficacy analysis.
- The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up. The change in eGFR from pretreatment baseline to post-treatment follow-up was −2.34mL/min/1.73m^2/year with Jynarque™ versus −3.61mL/min/1.73m^2/year with placebo, corresponding to a treatment effect of 1.3mL/min/1.73m^2/year (P<0.0001). Jynarque™ resulted in a slower decline versus placebo in eGFR at 1 year (difference: 1.27mL/min/1.73m^2/year; P<0.001).

- Elevations in the alanine aminotransferase level (to >3 times the upper limit of the normal range) occurred in 38 of 681 patients (5.6%) in the Jynarque™ group and in 8 of 685 (1.2%) patients in the placebo group. Elevations in the aminotransferase level were reversible after stopping Jynarque™. No elevations in the bilirubin level of more than twice the upper limit of the normal range were detected.

Cost:

Product	Cost Per Unit	Cost Per 28 Days
Jynarque™ (tolvaptan) 45mg/15mg therapy pack	**$232.88**	**$13,041.28**
Jynarque™ (tolvaptan) 60mg/30mg therapy pack	**$232.88**	**$13,041.28**
Jynarque™ (tolvaptan) 90mg/30mg therapy pack	**$232.88**	**$13,041.28**
Samsca® (tolvaptan) 15mg*	$429.33	$12,021.24
Samsca® (tolvaptan) 30mg*	$445.38	$24,941.28

Unit = tablet
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.
*Samsca® FDA approved starting dose is 15mg once daily and titrated up to a maximum of 60mg once daily. Due to the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS program for Jynarque™.

Recommendations

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

Jynarque™ (Tolvaptan) Approval Criteria:

1. An FDA approved indication to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD); and
2. Member must be 18 years of age or older; and
3. Member must not have any contraindications to taking Jynarque™ including the following:
    a. Taking any concomitant strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, conivaptan); and
    b. A history of signs or symptoms of significant liver impairment or injury (does not include uncomplicated polycystic liver disease); and
    c. Uncorrected abnormal blood sodium concentrations; and
    d. Unable to sense or respond to thirst; and
    e. Hypovolemia; and
    f. Hypersensitivity to tolvaptan or any of its components; and
    g. Uncorrected urinary outflow obstruction; and
    h. Anuria; and
4. Member must not be taking any of the following medications concomitantly with Jynarque™:
    a. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, conivaptan); and
    b. Strong CYP3A inducers (e.g., rifampin); and

    c. OATP1B1/3 and OAT3 transporter substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide); and
    d. BCRP transporter substrates (e.g., rosuvastatin); and
    e. V_2-receptor agonists (e.g., desmopressin); and
5. Jynarque™ must be prescribed by a nephrologist or specialist with expertise in the treatment of ADPKD (or be an advanced care practitioner with a supervising physician who is a nephrologist or specialist with expertise in the treatment of ADPKD); and
6. Prescriber must agree to assess ALT, AST, and bilirubin prior to initiation of Jynarque™, at 2 weeks and 4 weeks after initiation, then monthly for 18 months, and every 3 months thereafter; and
7. Female members must not be pregnant and must have a negative pregnancy test prior to therapy initiation; and
8. Prescriber, pharmacy, and member must be enrolled in the Jynarque™ Risk Evaluation and Mitigation Strategy (REMS) program and maintain enrollment throughout therapy.

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Appendix L

Calendar Year 2017 Annual Review of Vimizim® (Elosulfase Alfa)

Oklahoma Health Care Authority
July 2018

Introduction[1,2]

The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by a deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), previously known as mucopolysaccharides. Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities. Mucopolysaccharidosis type IV A (MPS IVA and the less common type B) also known as Morquio syndrome is an autosomal recessive disorder that results from mutations in the gene encoding galactosamine-6-sulfatase (*GALNS*). Morquio syndrome is characterized by skeletal involvement. Patients typically present at approximately 1 year of age with short stature, primarily due to a shortened neck and trunk, and joint laxity; protuberant sternum and knock-knee deformity are common. The incidences of MPS IV A and B are approximately 0.22 (range 0.07 to 1.32) and 0.14 per 100,000 births, respectively. In severe forms, linear growth is minimal after 6 or 7 years of age, and death usually occurs in the third or fourth decade from cardiorespiratory failure. Mildly affected patients may survive into the seventh decade.

Vimizim® (elosulfase alfa) is a hydrolytic lysosomal GAG-specific enzyme indicated for patients with MPS IVA or Morquio A syndrome. The recommended dose is 2mg/kg administered once every week as an intravenous (IV) infusion over a minimum of 3.5 to 4.5 hours, based on infusion volume. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of the infusion. Elosulfase alfa has a boxed warning for life-threatening anaphylactic reactions that have occurred in some patients during infusions. The boxed warning also includes patients with acute respiratory illness; these patients require additional monitoring as they may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions. It is recommended that elosulfase alfa be prepared and administered under the supervision of a healthcare professional with the ability to manage medical emergencies. Vimizim® is supplied as 5mg/5mL single-use vials.

Current Prior Authorization 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.

Utilization of Vimizim® (Elosulfase Alfa): Calendar Year 2017

There was no SoonerCare utilization of Vimizim® (elosulfase alfa) during calendar year 2017.

Prior Authorization of Vimizim® (Elosulfase Alfa)

There were no prior authorization requests submitted for Vimizim® (elosulfase alfa) during calendar year 2017.

Recommendations

The College of Pharmacy does not recommend any changes to the Vimizim® (elosulfase alfa) prior authorization criteria at this time.

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Appendix M

Calendar Year 2017 Annual Review of Brineura® (Cerliponase Alfa)

Oklahoma Health Care Authority
July 2018

Introduction[1,2,3]

Ceroid lipofuscinosis type 2 (CLN2) disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), collectively referred to as Batten disease. CLN2 disease is a rare inherited disorder caused by mutations in the *TPP1* gene. The *TPP1* gene provides instructions for producing an enzyme found in lysosomes called tripeptidyl peptidase-1 (TPP-1). A reduction in TPP-1 results in the incomplete breakdown of certain peptides that primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms typically begin between ages 2 and 4 years. The initial symptoms usually include language delay, recurrent seizures (epilepsy), and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects essential motor skills, such as sitting and walking. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. Batten disease is relatively rare, occurring in an estimated 2 to 4 of every 100,000 live births in the United States.

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. 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. Cerliponase alfa is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. The recommended dosage is 300mg administered once every other week as an intraventricular infusion followed by infusion of intraventricular electrolytes given over approximately 4.5 hours. Cerliponase alfa should be administered by, or under the direction of, a physician knowledgeable in intraventricular administration.

Current Prior Authorization 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.

Utilization of Brineura® (Cerliponase Alfa): Calendar Year 2017

There was no SoonerCare utilization of Brineura® (cerliponase alfa) during calendar year 2017.

Prior Authorization of Brineura® (Cerliponase Alfa)

There were no prior authorization requests submitted for Brineura® (cerliponase alfa) during calendar year 2017.

Market News and Updates[4,5]

News:

- **February 2018:** The National Institute for Health and Care Excellence (NICE) published draft guidance that did not recommend the drug cerliponase alfa for children with CLN2. Dr. Peter Jackson, chair of the independent Highly Specialised Technology committee, said: "The committee agreed that, although cerliponase alfa is not a cure for CLN2 disease, it is an innovative treatment that is effective in the short-term in slowing the rate at which it progresses. Given the significant burden this disease places on parents and carers of children with the condition, and the subsequent negative impact this can have on the quality of their lives, anything that can help to improve the treatment of these children is to be welcomed. However, in the absence of long-term evidence about its effectiveness in stabilising the disease and preventing death, and having taken all the health and non-health-related benefits of cerliponase alfa into account, the committee considered that the drug was not a good use of NHS* resources."[4]
  * National Health Services of England

- **April 2018:** BioMarin Pharmaceutical Inc. announced that *The New England Journal of Medicine* (*NEJM*) published updated results from a multi-center, open-label, dose-escalation and ongoing extension study evaluating the efficacy and safety of Brineura® (cerliponase alfa) in children with CLN2 disease in the May 2018 issue. The new data demonstrated that treatment with Brineura® resulted in less decline in motor and language function compared to historical controls.

Recommendations

The College of Pharmacy does not recommend any changes to the Brineura® (cerliponase alfa) prior authorization criteria at this time.

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Appendix N

Calendar Year 2017 Annual Review of Radicava® (Edaravone)

Oklahoma Health Care Authority
July 2018

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

Amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) is a rapidly progressive neurodegenerative disease that affects motor neurons in the brain and spinal cord that control voluntary muscle movement. The progressive degeneration of motor neurons in ALS eventually leads to their demise, and thus 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. Most people with ALS die from respiratory failure, usually within 3 to 5 years from 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 15,000 people in the United States have ALS, with an estimated prevalence of 5 cases per 100,000 population.[6] 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. There is currently no cure for ALS, and treatment typically consists of symptomatic and supportive care. Rilutek® (riluzole oral tablets) was approved by the U.S. Food and Drug Administration (FDA) in 1995 for the treatment of ALS and may prolong survival by a few months, but does not reverse the damage already done to motor neurons.

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".[7] Edaravone is the first new treatment for ALS approved by the FDA in over 20 years. Edaravone is a free radical scavenger that is thought to reduce oxidative stress, a likely factor in the onset and progression of ALS. Radicava® is supplied for intravenous (IV) infusion in single-dose bags containing 30mg of edaravone in 100mL of clear, colorless aqueous solution. The recommended dosing regimen is an IV infusion of 60mg edaravone administered over a 60 minute period. The initial dosing cycle should consist of daily dosing for 14 days, followed by a 14-day drug-free period. Subsequent dosing cycles should consist of daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

Radicava® became available in the United States in August 2017; the Drug Utilization Review (DUR) Board voted to prior authorize Radicava® in September 2017. The wholesale acquisition cost (WAC) of Radicava® is $1,086.00 per infusion, resulting in an annual cost of $141,180.00, based on 13 treatment cycles of maintenance dosing (10 infusions per 28-day treatment cycle).

Current Prior Authorization 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.

Utilization of Radicava® (Edaravone): Calendar Year 2017

There was no SoonerCare utilization of Radicava® (edaravone) during calendar year 2017.

Prior Authorization of Radicava® (Edaravone)

There were no prior authorization requests submitted for Radicava® (edaravone) during calendar year 2017.

Market News and Updates[8,9,10,11,12,13,14,15,16,17,18,19]

Anticipated Patent Expiration(s):

- Radicava® (edaravone): May 2024

News:

- **February 2018:** Researchers suggest that men frequently exposed to diesel exhaust may have a higher risk of ALS. Men in Denmark who had any exposure to diesel exhaust in their jobs 10 years before their ALS diagnosis were 20% more likely to have ALS than men with no diesel exhaust exposure. In the Denmark-based study, researchers studied 1,639 people from the Danish National Patient Registry who were diagnosed with ALS from 1982 to 2013, matching each person with ALS with 100 people of the same age and sex who did not have the disease. They calculated diesel exhaust exposure for each person using a job exposure matrix, incorporating potential hazards for specific workers like service station attendants, bus drivers, and construction workers. They calculated cumulative exposure up to 5 and 10 years before the ALS diagnosis time period. Researchers found that the adjusted odds ratio for ALS among men with an occupational diesel exhaust exposure increased with increasing lag periods. Men in occupations with the highest exposure had higher odds of ALS. The researchers saw no associations among women, but noted that specific tasks performed even in the same job can differ substantially between men and women. The reason for the association

between diesel exhaust and ALS is unclear; however, previous studies have demonstrated diesel exhaust can damage DNA, potentially resulting in mutations and subsequent cellular death and tissue damage, and animal models have shown a direct link between diesel exhaust exposure and neuroinflammation, which when experienced repeatedly, becomes neurotoxic and can lead to neurodegeneration in the central nervous system. This research comes on the heels of similar findings from the Netherlands which linked long-term exposure to traffic-related air pollution, including diesel exhaust, to increased ALS susceptibility.

- **April 2018:** An online model based on eight variables reliably predicted the personal survival outcome of patients with ALS, European researchers reported. Based on a study of 11,475 ALS patients from 14 European ALS centers from 1992 to 2016, the model predicted whether patients had very long, long, intermediate, short, or very short times between symptom onset and a composite outcome of noninvasive ventilation for more than 23 hours per day, tracheostomy, or death. Using baseline clinical, cognitive, and genetic variables defined at diagnosis, the researchers incorporated eight prognostic factors into the model: bulbar vs. non-bulbar onset, age at onset, definite vs. probable or possible ALS, diagnostic delay, forced vital capacity, progression rate, frontotemporal dementia, and the presence of a *C9orf72* repeat expansion. According to the researchers, they assessed the external validity of the model across several populations and showed that it has a probability of more than 95% for good performance. The online model is for physicians only, who must register to obtain access, and while ALS researchers may see the benefits of the model, clinicians should use caution, as there is not strong evidence regarding how to discuss diagnosis and prognosis appropriately and effectively. It is not known whether this statistical prediction tool outperforms expert clinicians, who were not involved in the study. Factors like psychological well-being and social support are not incorporated into the model, and it also doesn't account for treatments like riluzole, noninvasive ventilation, and gastrostomy placement.

Pipeline:

- **September 2017:** AB Science's masitinib added to therapy with riluzole slowed the rate of progression of ALS in terms of deterioration measured on the ALS Functional Rating Scale-Revised (ALSFRS-R) and by measures of quality of life, respiratory function, and survival. In the double-blind, placebo-controlled AB10015 study, patients aged 18 years or older who had disease duration of up to 36 months, had a forced vital capacity (FVC) of 60% or greater, and were receiving stable dosing with riluzole were randomly assigned 1:1:1 to masitinib 4.5mg/kg/day, masitinib 3mg/kg/day, or placebo, all with riluzole, for 48 weeks. Masitinib is an orally administered tyrosine kinase inhibitor that targets mast cells and macrophages through inhibiting a limited number of kinases. The European Medicines Agency (EMA) issued a negative opinion on the conditional marketing authorization for masitinib for the treatment of ALS in April 2018, which was submitted to the EMA in October 2016; AB Science is discussing the details required to obtain marketing authorization for masitinib with the EMA and is committed to carrying out the development of masitinib in the treatment of ALS. However, there have been

no updates published regarding the submission of a New Drug Application (NDA) to the FDA for masitinib. The FDA previously granted Orphan Drug designation to masitinib for the treatment of ALS in 2015.

- **November 2017:** Cytokinetics announced that VITALITY-ALS, the international Phase 3 clinical trial of tirasemtiv in patients with ALS, did not meet the primary endpoint of change from baseline in slow vital capacity (SVC) which was evaluated at 24 weeks following randomization; tirasemtiv also did not meet any of the secondary endpoints in the trial which were evaluated at 48 weeks. Serious adverse events were similar between patients who received tirasemtiv or placebo, but more patients discontinued double-blind treatment on tirasemtiv than on placebo primarily due to non-serious adverse events related to tolerability. The company has decided to suspend the development of tirasemtiv, a fast skeletal muscle troponin activator (FSTA). Cytokinetics also has a next-generation FSTA, CK-2127107, in an ongoing clinical development program in neuromuscular and non-neuromuscular disease and conditions associated with muscle dysfunction and weakness, including three Phase 2 trials currently underway in patients with ALS, spinal muscular atrophy (SMA), or chronic obstructive pulmonary disease (COPD), as well as a Phase 1b trial in elderly subjects with limited mobility.
- **November 2017:** The FDA notified Biohaven Pharmaceuticals that the company may proceed with its clinical investigation of sublingual BHV-0223 as a potential treatment for patients with ALS. BHV-0223 is an innovative sublingually administered and orally disintegrating tablet (ODT) formulation of riluzole. BHV-0223 is designed to be placed under the tongue, where it rapidly dissolves and is absorbed into the systemic circulation without the need for swallowing. The FDA previously granted Orphan Drug designation to BHV-0223 for the treatment of ALS in December 2016.
- **January 2018:** The FDA granted Orphan Drug designation to Aquestive Therapeutics' riluzole oral soluble film (OSF) for the treatment of ALS. Riluzole OSF is designed to dissolve instantly in the mouth without water. Riluzole OSF is currently in late-stage clinical development, with hope to bring the product to market in the second half of 2019.
- **March 2018:** The FDA granted Orphan Drug designation to Elysium Health's experimental product, EH301, for the treatment of ALS. The Orphan Drug designation submission included data from a 2017 double-blind, placebo-controlled European pilot study in humans. To expand on the results of the pilot study, Elysium Health expects to initiate a placebo-controlled study in collaboration with Mayo Clinic to evaluate EH301 in up to 150 adults with ALS by the fourth quarter of 2018.
- **June 2018:** Flex Pharma announced that it is stopping Phase 2 clinical trials of its investigational compound to ease muscle cramps, FLX-787, in patients with ALS or Charcot-Marie-Tooth (CMT) disease. The company's decision was based on oral tolerability concerns in each study with the ODT formulation at 30mg, taken three times daily. The company previously reported positive efficacy data in patients with ALS or multiple sclerosis (MS), showing the potential of FLX-787; however, recent observations of oral tolerability at the current dose and formulation in a subset of patients in both studies (ALS and CMT) indicate that more formulation and dose-ranging studies are

required. Flex Pharma is continuing to assess FLX-787 as a possible treatment for dysphagia. The FDA granted Fast Track designation to FLX-787 as a potential therapy for severe muscle cramps in patients with ALS in July 2017.

Recommendations

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

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Appendix O

Industry News and Updates

Oklahoma Health Care Authority
July 2018

Introduction

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

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

News:

- **Pregnant Women:** The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) approved 15 recommendations by majority vote on the inclusion and integration of pregnant and lactating women into clinical trials. The recommendations included removal of pregnant women as a vulnerable population in the common rule and the inclusion of pregnant and lactating women to capture and report maternal, obstetric, and neonatal outcomes. Catherine Spong, MD, deputy director of the National Institute for Child and Human Development (NICHD), stated, "execution [of these recommendations] will be a bit difficult, since we don't know what the secretary [of Health and Human Services (HHS)] is going to do." HHS charged the task force with identifying gaps in research on lactating and pregnant women. Dr. Spong emphasized that more work is needed on "prioritization" in terms of how they would like to present the recommendations to HHS, which will be incorporated into a full draft report. A finalized document is expected to be sent to the National Institutes of Health (NIH) executive secretary in June 2018 and to HHS and Congress in September 2018. The HHS secretary is required to act on the recommendations in December 2018. The task force included members of multiple government agencies, including individuals from the NIH, NICHD, the U.S. Food and Drug Administration (FDA), and the National Vaccine Program Office. Members of various professional organizations, such as the American Academy of Pediatrics, as well as members of industry also participated.
- **Gene Therapies:** According to the FDA Commissioner, Scott Gottlieb, MD, the FDA will soon be advising companies that certain gene therapies in development can qualify for a faster path to approval review. The FDA will first target hemophilia with its new policy. A spokesperson for the FDA stated that hemophilia was chosen because "it's an area of a lot of development activity." Gene therapies for hemophilia could be evaluated based on whether the therapy increases clotting factor in the blood, regardless of whether the therapy actually causes the patient to bleed less. Dr. Gottlieb said that a company might be required to perform more studies after the drug is on the market to make sure the initial sign of success actually pans out. For hemophilia, a company may have to demonstrate, after a product is on the market, that it actually reduces bleeding.

- **Diabetes:** According to Scandinavian researchers, adult-onset diabetes consists of five types of disease, rather than the traditional type 1 and 2 classification. After gathering data on approximately 15,000 patients from across five cohorts in Sweden and Finland, researchers found that using six standard measurements identified five clusters of patients with diabetes. These five clusters divided into three severe and two mild forms of disease, with one corresponding to type 1 diabetes and the other four representing subtypes of type 2 diabetes. The clusters included one of very insulin-resistant individuals at significantly higher risk of diabetic nephropathy, one of relatively young insulin deficient individuals with poor metabolic control, and a large group of elderly patients with the most benign disease course. The variables included the presence of glutamate acid decarboxylase antibodies; age at diagnosis; body mass index; hemoglobin A1c (HbA1c); and homeostatic model assessment (HOMA) 2 estimates of beta-cell function and insulin resistance, based on C-peptide concentrations calculated using the HOMA calculator. The research was published online in *The Lancet Diabetes and Endocrinology* and could have important implications in not only the diagnosis and management of diabetes, but future therapeutic guidance.
- **Product Labels:** The FDA issued new guidance for industry on how pharmaceutical companies can talk with payers, the public, and prescribers about new findings not included in a product's approved labeling. The new guidance addresses issues that pharmaceutical companies would like to discuss, "such as data from post-marketing studies and surveillance of a product's approved uses, or additional information from the pre-market studies that were used to support approval of the product," Scott Gottlieb, MD, FDA Commissioner, stated. However, the information must be "consistent" with the product's current labeling and is not intended for companies to discuss unapproved uses of their products. Other FDA announcements included industry communications with payers about their products' value in terms of cost-effectiveness; new guidance on inclusion of patient viewpoints in drug development; and a review by Dr. Gottlieb of the FDA's efforts to combat antimicrobial-resistant infections.

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Appendix P

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

FDA NEWS RELEASE

For Immediate Release: June 4th, 2018

FDA approves first biosimilar to Neulasta® to help reduce the risk of infection during cancer treatment

The FDA approved Fulphila™ (pegfilgrastim-jmdb) as the first biosimilar to Neulasta® (pegfilgrastim) to decrease the chance of infection as suggested by febrile neutropenia (fever, often with other signs of infection, associated with an abnormally low number of infection-fighting white blood cells), in patients with non-myeloid (non-bone marrow) cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia.

Biological products are generally derived from a living organism and can come from many sources, such as humans, animals, microorganisms or yeast. A biosimilar is a biological product that is approved based on data showing that it is highly similar to a biological product already approved by the FDA (reference product) and has no clinically meaningful differences in terms of safety, purity, and potency (i.e., safety and effectiveness) from the reference product, in addition to meeting other criteria specified by law.

The FDA's approval of Fulphila™ is based on review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates Fulphila™ is biosimilar to Neulasta®. Fulphila™ has been approved as a biosimilar, not as an interchangeable product.

The most common side effects of Fulphila® are bone pain and pain in extremities. Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products should not take Fulphila™.

Serious side effects from treatment with Fulphila™ include rupture of the spleen, acute respiratory distress syndrome, serious allergic reactions including anaphylaxis, acute inflammation of the kidney (glomerulonephritis), an abnormally high level of white blood cells (leukocytosis), capillary leak syndrome, and the potential for tumor growth. Fatal sickle cell crises have occurred.

The FDA granted approval of Fulphila™ to Mylan GmbH.

FDA NEWS RELEASE

For Immediate Release: June 25th, 2018

FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy

The FDA approved Epidiolex® (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients 2 years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC).

It is THC (and not CBD) that is the primary psychoactive component of marijuana.

Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.

Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5 years. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and

intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.
Epidiolex®'s effectiveness was studied in three randomized, double-blind, placebo-controlled clinical trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. Epidiolex®, taken along with other medications, was shown to be effective in reducing the frequency of seizures when compared with placebo.
The most common side effects that occurred in Epidiolex®-treated patients in the clinical trials were: sleepiness, sedation and lethargy, elevated liver enzymes, decreased appetite, diarrhea, rash, fatigue, malaise and weakness, insomnia, and infections.
Epidiolex® must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks. As is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks. Epidiolex® also caused liver injury, generally mild, but raising the possibility of rare, but more severe injury. More severe liver injury can cause nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine.
Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant. In support of this application, the company conducted nonclinical and clinical studies to assess the abuse potential of CBD.
The FDA prepares and transmits, through the U.S. Department of Health and Human Services, a medical and scientific analysis of substances subject to scheduling, like CBD, and provides recommendations to the Drug Enforcement Administration (DEA) regarding controls under the CSA. The DEA is required to make a scheduling determination.
The FDA granted Priority Review designation for this application. Fast-Track designation was granted for Dravet syndrome. Orphan Drug designation was granted for both the Dravet syndrome and Lennox-Gastaut syndrome indications.
The FDA granted approval of Epidiolex® to GW Research Ltd.

Safety Announcements

FDA Approves Labeling Supplement for Celebrex (celecoxib)

[06/28/2018] The FDA approved a labeling supplement for Celebrex® (celecoxib), a COX-2 selective non-steroidal anti-inflammatory drug (NSAID), to include results from a postmarketing cardiovascular (CV) outcomes trial that found that at the lowest dose, Celebrex® was similar to moderate doses of naproxen and ibuprofen with regard to CV safety.
The concerns about the CV thrombotic risk of COX-2 selective NSAIDS emerged in the early 2000's. Following an FDA Advisory Committee meeting held in 2005, in which data from large clinical outcome trials in a wide range of indications and epidemiology studies of several individual NSAIDs were considered, the FDA concluded that the risk for CV thrombotic events was present for both COX-2 selective NSAIDs and nonselective NSAIDs.
The "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen" (PRECISION) trial was conducted to address the remaining concerns about the relative CV safety of COX-2 selective NSAIDS and non-selective NSAIDs. PRECISION was a large, randomized, double-blind controlled trial that began in 2006. A total of 90% of the patients enrolled in the trial had osteoarthritis and the remaining 10% had rheumatoid arthritis.
The results of the PRECISION trial demonstrated that celecoxib at the lowest approved dose of 100mg twice daily, is non-inferior to (or no worse than) ibuprofen dosed in the range of 600mg - 800mg three times daily or naproxen dosed in the range of 375mg - 500mg twice daily on a composite CV endpoint consisting of CV death, nonfatal myocardial infarction, and nonfatal stroke.
In an ambulatory blood pressure monitoring study that was part of the larger PRECISION trial, celecoxib dosed at 100mg twice daily showed little effect on average 24-hour systolic blood pressure (SBP), whereas ibuprofen dosed in the range of 600mg - 800mg three times daily and naproxen dosed in the range of 375mg – 500mg twice daily increased average 24-hour SBP by 3.7mmHg and 1.6mmHg, respectively.
Too few patients received higher doses of Celebrex® to evaluate the risk of CV events or the effect on blood pressure for doses greater than 100mg twice daily. The cardiovascular risks of the NSAID class are dose-dependent, therefore, the results for celecoxib 100mg twice daily on the composite CV endpoint and the lack of effect on SBP cannot be extrapolated to dosing regimens using the higher strengths of celecoxib (200mg or

400mg). Patients with recent CV events such as acute MI, coronary revascularization, or coronary stent placement were not studied in the PRECISION trial. NSAID class labeling warns against the use of NSAIDs in such patients.
NSAIDs are effective treatments for pain, inflammation, and fever, yet should always be dosed at the lowest effective dose for the shortest duration necessary. Postmarketing safety studies such as the PRECISION trial can add valuable information to our understanding of drug safety issues that emerge in the postmarketing period, and we provide this information to give health care providers a better understanding of the NSAIDs' drug safety profile. Patients should talk to their doctor if they have any questions or concerns about prescription or over-the-counter NSAIDs, and always inform the doctor about their complete medical history, including any history of CV disease or stomach ulcers.

Current Drug Shortages Index (as of June 28th, 2018):

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

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

Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Fluorescein Strips	***Currently in Shortage***
Folic Acid Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Guanfacine Hydrochloride Tablets	***Currently in Shortage***
Heparin Sodium and Sodium Chloride 0.9% Injection	***Currently in Shortage***
Hydromorphone Hydrochloride Injection, USP	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Isocarboxazid Tablets	***Currently in Shortage***
Ketamine Injection	***Currently in Shortage***
Ketorolac Tromethamine Injection	***Currently in Shortage***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Leuprolide Acetate Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) and Dextrose Injection Solution-Premix Bags	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Lorazepam Injection, USP	***Currently in Shortage***
Magnesium Sulfate Injection	***Currently in Shortage***
Methadone Hydrochloride Injection	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methylphenidate Hydrochloride (QuilliChew ER) Extended-Release Chewable Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (Quillivant XR) for Extended-Release Oral Suspension	***Currently in Shortage***
Metoclopramide Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Molindone Hydrochloride Tablets	***Currently in Shortage***
Morphine Sulfate Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Ondansetron Hydrochloride Injection	***Currently in Shortage***
Pantoprazole (Protonix) Powder for Injection	***Currently in Shortage***
Penicillamine (Depen) Titratable Tablets	***Currently in Shortage***
Penicillin G Benzathine and Penicillin G Procaine (Bicillin C-R) Injection	***Currently in Shortage***
Penicillin G Procaine Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Phenytoin Sodium Injection, USP	***Currently in Shortage***
Phosphate Injection Products	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Progesterone Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	***Currently in Shortage***
Rocuronium Bromide Injection	***Currently in Shortage***
Ropivacaine Hydrochloride injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***

Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sodium Chloride Injection USP, 0.9% Vials	***Currently in Shortage***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Sterile Water	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Thioridazine Hydrochloride Tablets	***Currently in Shortage***
Zolpidem Tartrate (Edluar) Sublingual Tablets	***Currently in Shortage***