Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 26th, 2019 1:00 - 5:00 PM
DXC Conference Room
4070 27th Ct. SE
Salem, OR 97302
MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333.

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	T. Klein (Chair)
	D. Department Update	D. Weston (OHA)
1:10 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
	A. Muscle Relaxants, Oral Literature Scan	
	B. Herpes Simplex Virus Literature Scan	
	C. Insulins Class Update	
	D. Antidepressants - Reviewed in July 2019	
	1. Public Comment	
	III. PREFERRED DRUG LIST NEW BUSINESS	
1:15 PM	A. Drug Class Literature Scans	
	1. Hepatitis C, Direct-Acting Antivirals	M. Herink (OSU)
	2. Tobacco Smoking Cessation	D. Engen (OSU)
	3. Drugs for Duchenne Muscular Dystrophy	S. Servid (OSU)
	4. Public Comment	
	5. Discussion of Clinical Recommendations to OHA	
1:30 PM	B. Oral Cystic Fibrosis Modulators Prior Authorization Update	M. Herink (OSU)
	1. Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

1:40 PM	C. Opioid Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:05 PM	D. Vyndaqel® and Vyndamax® (tafamidis) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:20 PM	E. Spinal Muscular Atrophy Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Zolgensma® (onasemnogene abeparvovec-xioi) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:50 PM	BREAK	
3:00 PM	F. Bone Metabolism Drugs Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Evenity™ (romosozumab-aqqg) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:15 PM	G. Drugs for Fabry Disease Class Review 1. Fabrazyme® (agalsidase beta) Drug Evaluation 2. Galafold™ (migalastat) New Drug Evaluation 3. Prior Authorization Criteria 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:45 PM	H. Aemcolo™ (rifamycin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
4:00 PM	IV. EXECUTIVE SESSION	
4:50 PM	V. RECONVENE for PUBLIC RECOMMENDATIONS	
	VI. ADJOURN	
	VII. OHA RULES ADVISORY COMMITTEE 1. Public Comment	J. Torkelson (OHA)

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
Kelley Burnett, DO	Physician	Pediatrician / Associate Medical Director	Grants Pass	December 2019
Dave Pass, MD	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2019
Tracy Klein, PhD, FNP	Public	Nurse Practitioner	Portland	December 2020
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director	Coos Bay	December 2020
William Origer, MD	Physician	Residency Faculty	Albany	December 2020
James Slater, PharmD	Pharmacist	Pharmacy Director	Beaverton	December 2020
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, July 25, 2019 1:00 - 5:00 PM

DXC Conference Room

4070 27th Ct. SE

Salem, OR 97302

MEETING AGENDA

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333

Members Present: Tracy Klein, PhD, FNP; Mark Helm, MD, MBA, FAAP; William Origer, MD; Cathy Zehrung, RPh; James Slater PharmD

Members Present by Phone: Kelly Burnett, D.O.; Dave Pass, MD; Jim Richards MD, MBA

Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen; Victor Rojo

Staff Present by Phone: Kathy Sentena PharmD; Megan Herink, PharmD

Audience: *Mae Kwong, Johnson & Johnson; Trent Taylor, Johnson & Johnson; Michael Moore, PhD, Otsuka Pharmaceuticals; Leslie Far, Johnson & Johnson; Darlene Bitel, Takeda; *Jeffrey Nesheim, Pharm.D., Sage Therapeutics; Troy Larsen, Sage Therapeutics; Danielle Shannon, WVP Health; Rick Frees, Vertex Pharmaceuticals; *Sami Nasrawi, Alnylam Pharmaceuticals; Jon Taylor, Alnylam Pharmaceuticals; Laura Jeffcoat, Abbvie; Steve Isaki, Lundbeck; Rick Dabner, Alnylam Pharmaceuticals; Dennis Schaffer, Genzyme; Whitney Acoba; Paul Williams; Geetika Gupta, Merck; *Dan Allen, Genzyme; Mo Yang, Jazz Pharmaceuticals; Valerie Ng, Indivior; Georgette Dzwilewski, Indivior; *Deb Profant Jazz Pharmaceuticals, *Ryan Fowler, Pfizer; Pierre Thoumsin, Heron Therapeutics; Gordon Andringa, Jazz Pharmaceuticals

(*) Provided verbal testimony

Written testimony provided: Posted to OSU Website

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I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.
B. Conflict of Interest Declaration - No new conflicts of interest were declared.
C. Approval of May 2019 minutes presented by Mr. Citron and proposal to amend agenda to change order of presentation.
ACTION: Motion to approve, 2nd, all in favor
D. Department Update
No updates
E. Legislative Update
Dee Weston presented:

SB 138

- Reestablishes the mental health clinical advisory group in perpetuity
- Expands that membership of the MHCAG to include a representative from Dept. of Corrections, the tribes, and makes formal connection to the Oregon Psychiatric Advice Line
- Provides permanent staff support to the group
- Expands the MG drug carve out to Jan. 1, 2022

HB 2678:

With failure of HB 2678 this past session, we are evaluating our options going forward. This requires OHA to pause efforts toward an aligned PDL, which was originally intended to begin January 1, 2020. After OHA evaluates possible options moving forward, the agency will begin working with key partners and stakeholders to determine what is the best for OHP members, their providers and OHA.

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
B. CMS Annual Report
C. Inhaled Short-acting Beta-agonists Literature Scan
Recommendation:
1. Make no changes to the preferred drug list (PDL) based on clinical evidence.
2. Evaluate comparative drug costs in executive session.

ACTION: Motion to approve, 2nd, all in favor

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III. DUR ACTIVIES

A. ProDUR Report - Mr. Holsapple presented the ProDUR report & Support Act implications – expand ProDUR
B. RetroDUR Report - Dr. Engen presented the RetroDUR Report
C. Oregon State Drug Reviews
   1. Non-statin Low-Density Lipoprotein Cholesterol (LDL-C) Lowering Therapy and Cardiovascular Outcomes
   2. Update on Medications Used to Manage Opioid Use Disorder and Opioid Withdrawal

Dr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters.

IV. DUR NEW BUSINESS

A. Opioid/Sedative Retrospective DUR Proposal
   Dr. Engen presented the proposal to:
   1. Send a prescriber letter to notify them of combination opioid/sedative prescribing for patients with the following characteristics:
      a. Patients with 3 or more unique prescribers of opioid and sedative therapy
      b. Patients with a prior history of sedative poisoning

ACTION: The Committee recommended **e**xploring tools beyond the lettering to providers and members including developing dashboards and to aggregate data to consider sorting patients by timeframe. Targeting those with chronic issues; consider adding a profile list of meds.
Motion to approve, 2nd, 5 in favor, 3 opposed

V. PREFERRED DRUG LIST NEW BUSINESS

A. Antidepressant Class Update and New Drug Evaluation
   Dr. Sentena presented the proposal to:
   1. Make no changes to the PDL based on the review of clinical efficacy.
   2. Implement proposed prior authorization (PA) criteria for brexanolone and esketamine based on safety concerns.
   3. Evaluate comparative costs in executive session.

ACTION: The Committee recommended adding a question to the esketamine safety edit to ask about history of substance abuse and recommended referral to the MHCAG to investigate recently approved drugs and optimal treatments for kids.

Motion to approve, 2nd, all in favor

B. Transthyretin Mediated Amyloidosis New Drug Evaluations
Dr. Herink presented the proposal to:
1. Create a PDL class for Drugs for hATTR.
2. Designate inotersen and patisiran as non-preferred medications.
3. Implement clinical PA criteria for patisiran and inotersen to ensure appropriate utilization.

ACTION: The Committee recommended adding a question on baseline disease severity and to document genotype.
Motion to approve, 2nd, all in favor

C. Atopic Dermatitis (AD) Class Update and Dupilumab Drug Update
Dr. Moretz presented the proposal to:
1. Remove dupilumab from the atopic dermatitis and topical antipsoriatic PA criteria and create a new PA document for dupilumab utilization in moderate-to-severe asthma and moderate-to-severe AD.
2. Update PA criteria for dupilumab based on FDA approved ages for AD and add renewal criteria.
3. Reorder questions in the dupilumab PA criteria to assess the prescribing practitioner at the beginning of the PA review.
4. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd, all in favor

D. Narcolepsy Agents DERP Summary and New Drug Evaluation
Dr. Servid presented the proposal to:
1. Add solriamfetol as a voluntary non-preferred product to the Other Stimulants class.
2. Designate sodium oxybate as non-preferred based upon the current review of efficacy and safety data.
3. Recommend implementation of a safety edit for solriamfetol
4. Update safety edits for modafinil/armodafinil to include assessment of first-line therapy in patients with OSA and alternative options for treatment in children.

ACTION: The Committee recommended adding a question to require trial and failure of first-line therapies (e.g., methylphenidate).
Motion to approve, 2nd, all in favor

Topics Deferred to a Future Meeting

E. Bone Metabolism Class Update and New Drug Evaluation

F. Aemcolo™ (rifamycin) New Drug Evaluation

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VI. EXECUTIVE SESSION

Members Present: Mark Helm, MD, MBA, FAAP; Tracy Klein, PhD, FNP; William Origer, MD; Cathy Zehrung, RPh; James Slater, PharmD

Members Present by Phone: Stacy Ramirez, PharmD; David Pass, MD; Kelly Burnett, DO; Kathy Sentena, PharmD;

Staff Present: Roger Citron, RPh; David Engen, PharmD, CGP; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen; Victor Rojo

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Inhaled Short-acting Beta-agonists Literature Scan
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Antidepressant Class Update and New Drug Evaluation
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Atopic Dermatitis (AD) Class Update and Dupilumab Drug Update
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

VIII. ADJOURN

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Drug Class Literature Scan: Muscle Relaxants, Oral

Date of Review: September 2019

Date of Last Review: March 2017
Literature Search: 01/01/17 – 07/25/19

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There was no new clinical efficacy or safety evidence that would change current policy.
- There is no evidence to support using baclofen for alcohol use disorder (AUD) based on a good-quality systematic review and meta-analysis.[1]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on a review of the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- Review of the muscle relaxant class in 2017 resulted in no changes to the PDL. Previous reviews have demonstrated no differences in the clinical efficacy between skeletal muscle relaxants for musculoskeletal conditions.
- Evidence is insufficient to draw firm conclusions regarding the comparative effectiveness between baclofen, tizanidine or dantrolene for spasticity.
- The skeletal muscle relaxants, tizanidine, cyclobenzaprine, and baclofen are more efficacious than placebo for short-term (5 to 7 days) pain relief of acute low back pain (LBP).
- Dantrolene and chlorzoxazone are associated with rare serious dose-related hepatotoxicity.
- Prior authorization (PA) criteria limits the use of muscle relaxant therapy to 3 months due to insufficient evidence of efficacy beyond 5-7 days. The use of carisoprodol is limited to an equivalent of a two weeks supply (56 tablets), which is consistent with prescribing information, every 90 days. Prior authorization criteria is also in place to prevent the use of carisoprodol with opioids due to safety concerns. There were no claims for carisoprodol last quarter.
- Preferred therapies in the class are: baclofen, cyclobenzaprine and tizanidine.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the

Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane – Baclofen for Alcohol Use Disorder
A 2018 Cochrane review identified 12 randomized controlled trials evaluating the use of baclofen (10 mg to 150 mg daily) for AUD.[1] The mean patient age was 48 years old and 68% were male. The trials were small, 100 patients or less, and all patients had a diagnosis of alcohol dependence and were currently using alcohol. Eleven of the trials compared baclofen to placebo and there was one active treatment comparison of baclofen to acamprosate. All of the included trials were found to be at low risk of bias for all domains.[1]

For the primary outcome of relapse-return to any drinking, the efficacy for baclofen was similar to placebo (RR 0.88; 95% CI, 0.74 to 1.04; p=0.002) based on moderate quality evidence from 5 trials; however, heterogeneity was high (I^2=77%).[1] There was moderate quality evidence that for the outcome of percent of heavy drinking days at the end of treatment the results for baclofen and placebo were similar with a MD of 0.25 (95% CI, -1.25 to 1.76) based on 3 trials.[1] There was high quality evidence that there was no difference between baclofen and placebo for the outcomes of at least one adverse event, dropout rate at the end of treatment and dropouts due to adverse events. There was low evidence for the outcomes of frequency of use by the percentage of days abstinent. Overall, there was no differences between baclofen and placebo for outcomes related to alcohol use disorder.

After review, eleven systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

NICE – Cerebral Palsy
NICE released guideline recommendations for the management and treatment of cerebral palsy in adults in 2019.[2] Pharmacotherapy recommendations were provided for spasticity and dystonia. Treatments for spasticity included: enteral baclofen and enteral diazepam. The recommendation for enteral baclofen was based on limited evidence in children and young adults. NICE recommends against the use of enteral diazepam due to no evidence of efficacy and side effects such as drowsiness, vomiting and abdominal pain; however, acute, short-term use for pain and anxiety may be appropriate.[2] Intrathecal baclofen was determined to be appropriate for spasticity or dystonia in adults if managed by a specialty service. Overall, there was limited evidence for drug treatment for spasticity and dystonia in patients with cerebral palsy.[2]

New Formulations:
None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Metaxalone[3]	Skelaxin®	3/2018	Adverse reactions	CNS: cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range and with metaxalone as a single agent taken at doses higher than the recommended dose.

References:

1. Minozzi S, Saulle R, Rosner S. Baclofen for alcohol use disorder. *Cochrane Database of Systematic Reviews*. 2018;1:CD012557. doi:10.1002/14651858.CD012557.pub2
2. National Institute for Health and Care Excellence. Cerebral palsy in adults. January 15, 2019. Available at: Nice.org.uk/guidance/ng119. Accessed July 5, 2019.
3. Skelaxin Prescribing Information. Corepharma LLC, Middlesex, NJ. 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
baclofen	BACLOFEN	TABLET	Y
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL	TABLET	Y
tizanidine HCl	TIZANIDINE HCL	TABLET	Y
tizanidine HCl	ZANAFLEX	TABLET	Y
carisoprodol	CARISOPRODOL	TABLET	N
carisoprodol	SOMA	TABLET	N
carisoprodol/aspirin/codeine	CARISOPRODOL-ASPIRIN-CODEINE	TABLET	N
chlorzoxazone	CHLORZOXAZONE	TABLET	N
chlorzoxazone	LORZONE	TABLET	N
cyclobenzaprine HCl	AMRIX	CAP ER 24H	N
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL ER	CAP ER 24H	N
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL	TABLET	N
cyclobenzaprine HCl	FEXMID	TABLET	N
dantrolene sodium	DANTRIUM	CAPSULE	N
dantrolene sodium	DANTROLENE SODIUM	CAPSULE	N
metaxalone	METAXALL	TABLET	N
metaxalone	METAXALONE	TABLET	N
metaxalone	SKELAXIN	TABLET	N
methocarbamol	METHOCARBAMOL	TABLET	N
methocarbamol	ROBAXIN-750	TABLET	N
orphenadrine citrate	ORPHENADRINE CITRATE ER	TABLET ER	N
orphenadrine/aspirin/caffeine	NORGESIC FORTE	TABLET	N
orphenadrine/aspirin/caffeine	ORPHENGESIC	TABLET	N
tizanidine HCl	TIZANIDINE HCL	CAPSULE	N
tizanidine HCl	ZANAFLEX	CAPSULE	N
baclofen	BACLOFEN	TABLET	
chlorzoxazone	CHLORZOXAZONE	TABLET	

Appendix 2: New Comparative Clinical Trials

A total of twenty citations were manually reviewed from the initial literature search. After further review, twenty citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to July Week 2 2019

Search Strategy:

#	Searches	Results
1	Carisoprodol/	380
2	Chlorzoxazone/	432
3	cyclobenzaprine.mp.	264
4	dantrolene.mp. or Dantrolene/	2714
5	metaxalone.mp.	38
6	methocarbamol.mp. or Methocarbamol/	258
7	orphenadrine.mp. or Orphenadrine/	617
8	tizanidine.mp.	500
9	baclofen.mp. or Baclofen/	7261
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	12105
11	limit 10 to (english language and humans)	5084
12	limit 11 to yr="2017 -Current"	339
13	limit 12 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	22

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for skeletal muscle relaxants
Intervention	Muscle relaxant
Comparator	Active control or placebo
Outcomes	Pain relief, alcohol abstinence, reduced muscle spasticity
Timing	As indicated
Setting	Outpatient

Skeletal Muscle Relaxants

Goal(s):

- Cover non-preferred drugs only for funded conditions.
- Restrict carisoprodol to short-term use due to lack of long-term studies to assess safety or efficacy and high potential for abuse.

Length of Authorization:

- Up to 3 - 6 months

Requires PA:

- Non-preferred agents

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by the Oregon Health Plan?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Is drug requested carisoprodol?	**Yes:** Go to #5	**No:** Approve for up to 3 months
5. Has an opioid been prescribed within the past 30 days?	**Yes:** Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Does total quantity of carisoprodol exceed 56 tablets in 90 days? From claims, document product, dose, directions, and amount used during last 90 days.	**Yes:** Go to #7	**No:** Approve for up to 3 months
7. Does patient have a terminal illness (e.g. metastatic cancer, end stage Parkinson's disease, ALS)?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Go to #8

8. Pharmacist's statement:
 	
• Carisoprodol cannot be approved for long term usage.
• Patients are limited to 56 tablets in a 90 day period.
• It is recommended that the patient undergo a "taper" of the carisoprodol product of which a supply may be authorized for this to occur.
• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following:
  ○ >65 years of age; or
  ○ renal failure; or
  ○ hepatic failure; or
  ○ take > 1400 mg per day?
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350 mg TID X 3 days, then
	• 350 mg BID X 3 days, then
	• 350 mg daily x 3 days then evaluate
		No: Approve short taper:
		
		• Authorize 10 tablets
		• Reduce dose over 4 days
		• 350 mg TID x 1 day, then
		• 350 mg BID x 2 days, then
		• 350 mg daily x1 day, then evaluate

P&T Review: *9/19 (KS); 3/17 (DM); 3/17; 11/14; 9/09; 2/06; 2/04; 11/01; 2/01; 9/00; 5/00; 2/00*
Implementation: *4/1/17; 1/1/15, 1/1/14, 1/1/10, 11/18/04*

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Drug Class Literature Scan: Herpes Simplex

Date of Review: September 2019

Date of Last Review: July 2016
Literature Search: 01/01/2016 – 07/24/2019

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There was no new high quality evidence to evaluate since the last review done in 2016.

Recommendations:
- No changes to the preferred drug list are recommended. No further research is needed.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The evidence review done in 2016 found no new evidence demonstrating differences in efficacy or harms between antivirals used for herpes simplex.
- Acyclovir capsules, tablets and suspension are on the preferred drug list (PDL) for the class.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Author: Kathy Sentena, PharmD

New Systematic Reviews:
After review, two systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[1–3]

New Guidelines:
No new guidelines were identified.

New Formulations:
None identified

New FDA Safety Alerts:
None identified

References:
1. Forbes HJ, Williamson E, Benjamin L, et al. Association of herpesviruses and stroke: Systematic review and meta-analysis. *PLoS ONE [Electronic Resource]*. 2018;13(11):e0206163. doi:10.1371/journal.pone.0206163

2. Seo H-M, Kim YS, Bang CH, et al. Antiviral prophylaxis for preventing herpes zoster in hematopoietic stem cell transplant recipients: A systematic review and meta-analysis. *Antiviral Res*. 2017;140:106-115. doi:10.1016/j.antiviral.2017.01.011

3. Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes. *Cochrane Database Syst Rev*. 2016;(8):CD010684. doi:10.1002/14651858.CD010684.pub2

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
acyclovir	ACYCLOVIR	ORAL	CAPSULE	Y
acyclovir	ZOVIRAX	ORAL	CAPSULE	Y
acyclovir	ACYCLOVIR	ORAL	ORAL SUSP	Y
acyclovir	ZOVIRAX	ORAL	ORAL SUSP	Y
acyclovir	ACYCLOVIR	ORAL	TABLET	Y
acyclovir	ZOVIRAX	ORAL	TABLET	Y
acyclovir	ACYCLOVIR	TOPICAL	CREAM (G)	N
acyclovir	ZOVIRAX	TOPICAL	CREAM (G)	N
acyclovir	SITAVIG	BUCCAL	MA BUC TAB	N
acyclovir	ACYCLOVIR	TOPICAL	OINT. (G)	N
acyclovir	ZOVIRAX	TOPICAL	OINT. (G)	N
acyclovir/hydrocortisone	XERESE	TOPICAL	CREAM (G)	N
docosanol	ABREVA	TOPICAL	CREAM (G)	N
docosanol	DOCOSANOL	TOPICAL	CREAM (G)	N
famciclovir	FAMCICLOVIR	ORAL	TABLET	N
penciclovir	DENAVIR	TOPICAL	CREAM (G)	N
valacyclovir HCl	VALACYCLOVIR	ORAL	TABLET	N
valacyclovir HCl	VALTREX	ORAL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 59 citations were manually reviewed from the initial literature search. After further review, 59 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to July Week 2 2019

Search Strategy:

#	Searches	Results
1	acyclovir.mp. or Acyclovir/	10930
2	famciclovir.mp. or Famciclovir/	787

3	ganciclovir.mp. or Ganciclovir/	8090
4	valacyclovir.mp. or Valacyclovir/	1292
5	penciclovir.mp.	385
6	docosanol.mp.	88
7	herpes simplex.mp. or Herpes Simplex/	42350
8	1 or 2 or 3 or 4 or 5 or 6 or 7	54645
9	limit 8 to (english language and humans and yr="2016 -Current")	2837
10	limit 9 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	59

Appendix 4: Key Inclusion Criteria

Population	Patients with a diagnosis of herpes simplex
Intervention	Antiviral indicated for herpes simplex
Comparator	Placebo or active treatment
Outcomes	Resolution of virus
Timing	Infection onset
Setting	Outpatient

Antivirals for Herpes Simplex Virus

Goal(s):

- Cover oral and/or topical antivirals only for covered diagnoses.
- HSV infections are covered only when complicated by an immunocompromised host.

Length of Authorization:

- Up to 12 months (criteria specific)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [1–3]
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the diagnosis uncomplicated herpes simplex virus infection? ~~(B002; B0089; B001; B009)?~~	**Yes:** Go to #4	**No:** Go to #6

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr>
<td>4. Pass to RPh: Is the patient immunocompromised (document ICD10 code).
Examples:
• Diagnosis of cancer AND currently undergoing chemotherapy or radiation. Document therapy and length of treatment.
• Solid organ transplant
• HIV/AIDS</td>
<td>Yes: Approve for up to 12 months</td>
<td>No: Go to #5</td>
</tr>
<tr>
<td>5. Is the patient currently taking an immunosuppressive drug?

Document name of drug. If is drug not in the list below, pass to RPh for evaluation. Immunosuppressive drugs include, but are not limited to:
<table>
<tr><th colspan="2">Immunosuppressants</th></tr>
<tr><td>Abatacept</td><td>Infliximab</td></tr>
<tr><td>Adalimumab</td><td>Leflunomide</td></tr>
<tr><td>Anakinra</td><td>Methotrexate</td></tr>
<tr><td>Apremilast</td><td>Natalizumab</td></tr>
<tr><td>Azathioprine</td><td>Rituximab</td></tr>
<tr><td>Basiliximab</td><td>Secukinumab</td></tr>
<tr><td>Certolizumab pegol</td><td>Sirolimus</td></tr>
<tr><td>Cyclosporine</td><td>Tacrolimus</td></tr>
<tr><td>Cyclosporine</td><td>Tocilizumab</td></tr>
<tr><td>Etanercept</td><td>Tofacitinib</td></tr>
<tr><td>Golimumab</td><td>Ustekinumab</td></tr>
<tr><td>Hydroxychloroquine</td><td>Vedolizumab</td></tr>
</table>
</td>
<td>Yes: Approve for up to 90 days</td>
<td>No: Pass to RPh. Go to #6.</td>
</tr>
</table>

Approval Criteria		
6. RPh only: All other indications need to be evaluated as to whether they are an OHP-funded condition.	If funded and clinic provides supporting literature, approve for length of treatment. If length of treatment is not provided, approve for 3 months. Note: deny non-viral diagnoses (medical appropriateness)	If non-funded, deny (not funded by the OHP). Note: Deny viral ICD-10 codes that do not appear on the OHP funding list pending a more specific diagnosis code (not funded by the OHP).

P&T Review: *7/19 (KS), 7/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *8/16; 1/1/11*

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Salem, Oregon 97301-1079
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Drug Class Update: Diabetes, Insulins

Date of Review: September 2019

Date of Last Review: November 2018
Dates of Literature Search: 06/01/2017 – 05/27/2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to review new evidence on the efficacy and safety of insulin products published since the last review.

Research Questions:
1. In patients with diabetes mellitus (DM), is there any new comparative evidence for insulin therapies based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. In patients with DM, is there any new comparative evidence for non-insulin diabetes treatments based on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, etc.)?
3. Are there subpopulations of patients with DM for which specific therapies may be more effective or associated with less harm?

Conclusions:
- New high-quality evidence comes from three systematic reviews, five randomized controlled trials and one guideline. Four guidelines are available for clinical context. New evidence supports current policy of no clinically significant differences in glucose lowering between long-acting insulin products or between the short-acting insulin products.

Efficacy
- A high quality systematic review and meta-analysis found glucose lowering to be similar in patients with diabetes for insulin degludec, detemir and glargine, based on moderate to high strength of evidence.[1]
- World Health Organization (WHO) guidelines on second- and third-line therapies for non-pregnant adult patients with diabetes support current preferred drug list (PDL) recommendations for insulins.[2]
- Limited evidence suggests no difference in glucose lowering between glargine products in the elderly population, based on a study in patients 65 years and older which found glargine U100 to be noninferior to glargine U300 for the outcome of change in HbA1c from baseline at 26 weeks (least squares mean difference [LSMD] 0.02; 95% confidence interval [CI], -0.092 to 0.129).[3]

Author: Kathy Sentena, PharmD

Safety

- There is moderate quality evidence that there is no difference between adjudicated cardiovascular (CV) events in patients with type 2 diabetes mellitus (T2DM) at high risk of a cardiovascular (CV) events treated with insulin degludec compared to insulin glargine over 1.8 years (hazard ratio [HR] 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[4]
- Moderate strength of evidence found less hypoglycemia in patients treated with insulin degludec compared to insulin glargine. The difference of nocturnal hypoglycemia was less in patients with type 1 diabetes mellitus (T1DM) (relative risk [RR] 0.68; 95% CI, 0.56 to 0.81; p<0.05) and T2DM (RR 0.71; 95% CI, 0.63 to 0.79; p<0.05).[1] Severe hypoglycemia was also less with insulin degludec compared to insulin glargine in patients with T2DM.[1]

New Formulations

- A new fast-acting insulin aspart (FIASP®) was approved based on noninferiority findings compared to insulin aspart. The major difference is that FIASP can be given up to 20 minutes after the meal has started.[5]
- A new fast-acting follow-on to insulin lispro, Admelog®, was approved based on noninferiority findings.[6]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of clinical efficacy.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- A 2018 Drug Effectiveness Review Project report of long-acting insulins found moderate to high quality evidence that there were no clinically significant differences between the insulins for a majority of comparisons.
- Moderate to high quality evidence found no differences in HbA1c lowering between the long-acting insulin products. The DERP review found a reduced risk of hypoglycemia with insulin degludec compared to insulin glargine in patients with T1DM and T2DM.
- A review of Basaglar® demonstrated noninferiority to insulin glargine.
- No policy changes were made after reviewing evidence for the long-acting insulins in 2018. A 2017 review of insulin products resulted in removal of the PA requirement for insulin glargine (Lantus®) pens and insulin aspart (Novolog®). The requirement that patients must use 40 units or less per day of insulin to be candidates for an insulin pen was also removed to allow patients who use large amounts of insulin access to concentrated insulin products.
- Current preferred products are insulin aspart (cartridge, pen, vial, 70-30 mix), insulin detemir pen, insulin glargine (pen, vial), insulin lispro (vial, 50-50 mix, 75-25 mix), NPH (vial), regular insulin (vial) and NPH/R insulin (vial and pen) (**Appendix 1**).
- Short and long-acting insulins account for a substantial number of claims and costs to the OHP system. Approximately 86% of insulin utilization is for preferred products.

Background:

More than 29 million people in the United States are thought to be living with diabetes.[7] In Oregon, it is estimated that 287,000 adults have diabetes, in which 38,000 are thought to be OHP members. There are over 7,000 patients in the Oregon Medicaid fee-for-service population alone that have T2DM and almost 1,000 have T1DM.[8] Caring for patients with diabetes enrolled in OHP accounted for $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[8]

Insulin is used to mimic endogenous insulin release in patients with T1DM and is often necessary to obtain glucose targets in patients with T2DM. Adjustments in insulin doses are made to obtain target fasting and prandial glucose levels while minimizing the risk of hypoglycemia. Insulins are categorized by onset and duration of action. Most T1DM patients use multiple daily injections of basal and prandial insulins. Patients with T2DM who require insulin therapy are usually initiated on a basal insulin product. Basal insulins include NPH and recombinant analog formulations glargine, detemir, and degludec. Prandial insulins include formulations of regular insulin, and recombinant analogs lispro, aspart and glulisine. Evidence suggests no clinical differences in A1C lowering between the different basal insulins products in patients with T1DM or T2DM.[9] Hemoglobin A1C lowering has been shown to be similar between the different prandial insulins. Common insulin adverse reactions are hypoglycemia, injection site reactions, and weight gain. Basal insulin analogs and rapid-acting insulin analogs may have a reduced risk of hypoglycemia.[10] However, recent retrospective observational data from 25,489 patients found no clinically or statistically significant differences in hypoglycemia-related emergency department visits or hospital admissions between basal insulin analogs and NPH insulin (between group difference of 3.1 events per 1000 person-years (95% CI, -1.5 to 7.7; p=0.07).[11]

Clinically meaningful outcomes in patients with diabetes include microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular complications (i.e., stroke, myocardial infarction), mortality, and severe hypoglycemia. Because hyperglycemia is associated with increased microvascular complications and possibly macrovascular outcomes, A1C changes are often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies.[12] The Diabetes Control and Complication Trial (DCCT), which was a large prospective trial in patients with T1DM, provided evidence that intensive insulin therapy led to improved glucose control and reductions in microvascular outcomes.[13] A study in T2DM patients reiterated the DCCT findings, that maintenance of glucose lowering targets minimized microvascular complications in this population.[14] Due to the increased risk of CV disease in patients with diabetes, the effect of insulin on CV outcomes is of high importance. Evidence has shown that intensive glucose control produced a trend towards less risk of CV events in patients with T1DM.[13] In patients with T2DM intensive glucose control reduced CV outcomes based on the United Kingdom Prospective Diabetes Study (UKPDS) study; however, this was not shown in subsequent studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD], The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] and Veterans Affairs Diabetes Trial [VADT]]).[12] There is a paucity of evidence on the risk or benefit of insulin use on CV outcomes in patients with diabetes from randomized controlled trials (RCTs) specifically designed to assess CV events. One study compared insulin glargine to standard of care and n-3 fatty acids or placebo in patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. The study found similar rates of CV outcomes (nonfatal MI, nonfatal stroke, or death from CV causes) in both groups: 2.94 and 2.85 per 100 person-years in patients with a median follow-up of 6.2 years (HR 1.02; 95% CI, 0.94 to 1.11).[15] Cardiovascular effects were also similar between insulin degludec and insulin glargine in patients with T2DM at high risk for CV events, 8.5% versus 9.3% (HR 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[4]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane – Short-acting Insulin Analogues versus Regular Human Insulin

In 2018, Cochrane evaluated the short-acting insulins (insulin lispro, insulin aspart, insulin glulisine, or biosimilars) compared to regular insulin in adult, non-pregnant persons with T2DM.[16] Ten trials (n=2751) were included that were at least 24 weeks long (mean 41 weeks). All trials were open-label and five were non-inferiority trials. Patients were a mean age of 57 years, the average duration of diabetes was 13 years, baseline HbA1c was 8.1% and 45% were female.[16]

Mortality was described in 6 trials. Moderate quality evidence found no difference in deaths between regular insulin and insulin analogs, 0.2% and 0.4% (odds ratio [OR] 1.66; 95% CI, 0.41 to 6.64; P=0.48).[16] The mean difference in A1c was -0.3% lower with insulin analogs (95% CI, -0.15 to 0.09; p=0.43), which was not clinically or statistically significant.[16] The number of severe hypoglycemic events was low and similar between regular insulin and insulin analogs; however, evidence was limited. Evidence for all other outcomes were found to be of very low or low quality.

Limitations to the evidence include a high risk of detection and performance bias, due to the studies being an open-label design. Overall, there was no substantial difference between regular insulin and insulin analogs.

Cochrane – Treatments for Women with Gestational Diabetes Mellitus

A 2018 Cochrane systematic review and meta-analysis analyzed the efficacy and safety of therapies for women with gestational diabetes.[17] The review only included previous Cochrane Systematic Reviews and excluded women with pre-existing diabetes. Fourteen reviews were included, 10 of which were considered high-quality and had at low risk of bias.[17] Oral antidiabetic therapies included: glibenclamide (glyburide), metformin and acarbose. Included insulin therapies were insulin lispro, regular insulin and NPH insulin. Absolute risk reduction was not reported.

Moderate quality evidence found lifestyle interventions effectively reduced the infant outcome, large-for-gestational age, compared to usual care (RR 0.60; 95% CI, 0.50 to 0.71); however, lifestyle intervention versus usual care also increased the risk of induction of labor (RR 1.20; 95% CI, 0.99 to 1.46; moderate quality evidence).[17] Exercise versus control (no exercise) had no impact on assisting women in returning to their pre-pregnancy weight. The use of insulin versus oral therapy was found to possibly increase the risk of induction of labor (RR 1.3; 95% CI, 0.96 to 1.75) based on moderate quality of evidence.[17] Additionally, moderate quality of evidence found the use of insulin in pregnant women possibly increases the risk of hypertensive disorders in pregnancy (RR 1.89; 95% CI, 1.14 to 3.12).[17] The authors concluded that even though there is possible increase risk of induction of labor and hypertensive disorders, the overall body of evidence is insufficient to provide strong conclusions. Evidence was inconclusive for other outcomes (e.g., childhood adiposity, caesarean section, pre-eclampsia, perinatal mortality).

Holmes, et al – Comparative Effectiveness and Harms of Long-acting Insulins for Type 1 and Type 2 Diabetes

A good quality meta-analysis compared the efficacy and harms of long-acting insulins.[1] The review was commissioned by the Drug Effectiveness Review Project (DERP) and was conducted in accordance with the high-quality methodology utilized for the DERP reviews. The following interventions were included in the review: follow-on insulin glargine (Semglee), follow-on insulin glargine (Lusduna [approved but not available due to pending lawsuit] Nexvue [not available]), follow-on insulin glargine (U100) (Basaglar and Abasaglar), insulin degludec (U100 & U200) (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30), insulin glargine U300 (Toujeo), insulin detemir (Levemir), and insulin glargine U100 (Lantus). Seventy studies, lasting 16 weeks to 2 years, met the criteria for inclusion; 76% of fair quality, 12% good quality and 12% poor quality.[1] Outcomes of interest were: HbA1c, hypoglycemia (severe, nocturnal), withdrawals due to adverse events, cancer and cardiovascular events.

For a majority of comparisons there was low or insufficient evidence (**Table 1**).[1] Comparisons with moderate to high strength of evidence for selected outcomes are presented in **Table 2**. No statistical or clinical differences were found between insulin degludec, detemir, and glargine for the outcome of glucose lowering. Less hypoglycemia was found with insulin degludec compared to insulin glargine in patients with T1DM and T2DM. Patients taking insulin detemir experienced less weight gain (difference of approximately 1 kg) than patients taking insulin degludec or glargine; however, differences are unlikely to be clinically significant.

Table 1. Long-acting Insulin Comparisons with Low or Insufficient Evidence for All Outcomes Studied[1]

Insulin degludec/insulin aspart 70/30 vs. insulin detemir/insulin aspart	Insulin degludec/insulin aspart vs. insulin detemir/insulin aspart
Insulin degludec U200 vs. insulin degludec 100	Insulin degludec/insulin aspart 70/30 vs. insulin degludec/insulin aspart
Basaglar vs. insulin glargine	Insulin glargine pen vs. insulin glargine vial

Table 2. Long-acting Insulin Comparisons with Moderate to High Strength of Evidence[1]

Comparison	Outcome	Results*	Strength of Evidence
Adults with T1DM			
Insulin degludec + insulin aspart vs. Insulin glargine + insulin aspart	HbA1c	MD 0.07% (95% CI, -0.05 to 0.19) (4 RCTs; p>0.05) *No difference between treatments*	Moderate
	Nocturnal hypoglycemia	RR 0.68 (95% CI, 0.56 to 0.81; p<0.05) (4 RCTs) *Less nocturnal hypoglycemia with degludec compared to glargine*	Moderate
Insulin glargine U300 vs. insulin glargine U100	Nocturnal hypoglycemia	RR 0.91 (95% CI, 0.80 to 1.05; p<0.05) (RCTs 4) *No difference between treatments*	Moderate
Adults with T2DM			
Insulin degludec + insulin aspart vs. Insulin glargine + insulin aspart	Patients achieving an HbA1c <7%	RR 0.97 (95% CI, 0.91 to 1.03; p>0.05) (7 RCTs) *No difference between treatments*	High
	Severe hypoglycemia	RR 0.72 (95% CI, 0.54 to 0.96; p<0.05) (9 RCTs) *Less severe hypoglycemia with degludec compared to glargine*	Moderate
	Nocturnal hypoglycemia	RR 0.71 (95% CI, 0.63 to 0.79; p<0.05) (10 RCTs) *Less nocturnal hypoglycemia with degludec compared to glargine*	Moderate

	Major CV events	RR 0.92 (95% CI, 0.80 to 1.06; p>0.05) (4 RCTs) *No difference in CV events*	Moderate
Insulin degludec/insulin aspart 70/30 vs. insulin glargine (U100)	Patients achieving an HbA1c <7%	Insulin degludec/aspart: 43% Insulin glargine: 41% RR 1.04 (95% CI, 0.90 to 1.21; p>0.05) (2 RCTs) *No difference between treatments*	Moderate
Insulin detemir vs. insulin glargine	Withdrawals due to adverse events	RR 2.1 (95% CI, 1.4 to 3.3; p>0.05) (4 RCTs) *More withdrawals due to adverse events with detemir compared to glargine*	Moderate
Insulin glargine U300 vs. insulin glargine U100	Patients achieving an HbA1c <7%	Insulin glargine U300: 35% Insulin glargine U100: 35% RR 1.0 (95% CI, 0.92 to 1.1; p>0.05) (4 RCTs) *No difference between treatments*	Moderate
	Nocturnal hypoglycemia	Insulin glargine U300: 37% Insulin glargine U100: 50% RR 0.78 (95% CI, 0.59 to 1.03; p>0.05) (3 RCTs) *No difference between treatments*	Moderate
Key: * Absolute risk reductions included if reported Abbreviations: CI = confidence interval; CV = cardiovascular events; HbA1c = hemoglobin A1c; MD = mean difference; RCT = randomized controlled trial; RR = rate ratio; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus			

After review, seven systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

World Health Organizations – Guidelines on Second-and Third-line Diabetic Medicines and Type of Insulins

A 2018 WHO publication provided recommendations on the management of non-pregnant patients with diabetes.[2] The focus of the guideline is to provide recommendations for primary care providers in low resource settings. The guideline methodology was evaluated and found to be of high quality. This review will focus on recommendations for the use of insulin and will not cover oral therapies. Treatment recommendations are presented in **Table 3**.[2] The recommendation for human insulin is based on the lack of high quality evidence demonstrating that insulin analogues are more effective compared to human insulin. The recommendation for long-acting insulin analogues is considered weak because there is insufficient high-quality comparative evidence for diabetes complications and mortality demonstrating superior efficacy of the long-acting insulin analogues over intermediate-acting human insulin.

Table 3. WHO Recommendations for Insulin Use as a second- or third-line Treatment in Patients with Diabetes[2]

Recommendation	Strength of Recommendation and Quality of Evidence
• Introduce human insulin treatment to patients with T2DM who do not achieve glycemic goals with metformin and/or sulfonylurea	Strong recommendation; very low quality evidence
• Use human insulin (regular or NPH insulin) in adult patients with T1DM or T2DM who require insulin to manage glucose levels	Strong recommendation; very low quality evidence
• Consider using long-acting insulin analogues in adults with T1DM or T2DM who experience frequent severe hypoglycemia with human insulin	Weak recommendation; low or very low quality evidence
Abbreviations: NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus	

Additional Guidelines for Clinical Context:

The American Diabetes Association (ADA) published their annual Standards of Medical Care in Diabetes for 2019 in January.[18] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

A second guidance on the cardiovascular management of non-pregnant adults with diabetes was published by the ADA in April of 2018.[19] However, details are not included due to the same limitations cited above for the Standards of Medical Care in Diabetes.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2018.[10] Similar to the ADA recommendations, this management algorithm was authored by a majority of authors with industry affiliations and the methods for guideline development were not disclosed. Due to these limitations, the algorithm will not be presented.

The International Diabetes Federation (IDF) published clinical practice recommendations for managing type 2 diabetes in primary care.[20] Recommendations were based on worldwide diabetes treatment guidelines. Guidelines were graded by the Agree II instrument with scores ranging from 36-97%, indicating that low to high quality sources were considered in making recommendations. Therefore, the IDF recommendations will not be included in detail.

New Formulations or Indications:
FIASP – a new formulation of insulin aspart (FIASP®) was approved in 2017, indicated to improve glucose control in adults with diabetes.[5] The new formulation has a faster onset of action compared to insulin aspart, allowing for dosing at meal time or within 20 minutes of starting the meal. Trials found FIASP to be non-inferior to insulin aspart in patients with T1DM and T2DM.[5]

Admelog – A new fast-acting follow-on to insulin lispro was approved in 2017. Admelog® is approved for use in adults and pediatric patients 3 years and older with T1DM and T2DM to improve glycemic control. In clinical trials, Admelog® was found to be noninferior to insulin lispro.[6]

Label Changes:
Xultophy – the combination product, insulin degludec and liraglutide (Xultophy®), had the label updated in February 2019 to remove the requirement for previous therapy with either insulin or liraglutide.[21] Previous indications required a failure to one of these treatments.

Soliqua – removal of the requirement to fail monotherapy with insulin or lixisenatide before using the combination product, insulin glargine and lixisenatide (Soliqua™), was changed in the prescribing information in February of 2019.[22]

New FDA Safety Alerts:

Table 4. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Insulin human[23]	Afrezza	4/2018	Warnings and precautions	Lung cancer (2 cases in 2,750 patient-years of exposure) and 2 additional cases after clinical trial completion
Insulin degludec and liraglutide[21]	Xultophy	2/2019	Warnings and precautions	An increased incidence of acute events of the gallbladder was found in a recent trial, 3.1% for liraglutide and 1.9% for placebo

Randomized Controlled Trials:
A total of 226 citations were manually reviewed from the initial literature search. After further review, 221 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining five trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Klonoff, et al[24] DB, NI, TTT, RCT, Phase 3	Fast-acting insulin aspart (FA) CSQI Vs. Insulin aspart (A) CSQI 16 weeks	Patients with T1DM treated with CSQI (n=417)	Change from baseline HbA1c at 16 weeks	FA: -0.1% A: -0.1% ETD 0.09% (95% CI, 0.01 to 0.17; P<0.001) *Fast-acting aspart was non-inferior to aspart*
Marso, et al[4] DB, TTT, ED, RCT	Insulin degludec once daily Vs. Insulin glargine U100 once daily 1.8 years	Patients with T2DM and at high risk of cardiovascular events (n=7637)	Time to adjudicated major CV event (death from CV causes, nonfatal MI, or nonfatal stroke)	D: 325 (8.5%) G: 356 (9.3%) HR 0.91 (95% CI, 0.78 to 1.06; P<0.001 for noninferiority) *Insulin degludec was noninferior to insulin glargine for the risk of CV events*

Ritzel, et al[3] MC, OL, RCT, Phase 3b	Insulin glargine 300 u/mL (G300) Vs. Insulin glargine 100 u/mL (G100) 26 weeks	Patients 65 years and older (mean age 71 years) with T2DM (n=1014)	Change in baseline HbA1c at week 26	G300: -0.89% G100: -0.91% LSMD 0.02 (95% CI, -0.092 to 0.129) *Insulin glargine 300u/mL was non-inferior to insulin glargine 100 u/mL*
Rosenstock, et al[25] MC, OL, AC, PG, NI	Insulin glargine 300 u/mL (G300) Vs. Insulin degludec 100 u/mL (D100) 24 weeks	Insulin-naïve adult patients with uncontrolled T2DM (HbA1c of ≥7.5% or up to 10.5% on oral medication) (n=929)	Change in baseline HbA1c at 24 weeks	G300: -1.7% D100: -1.6% LSMD -0.5 (95% CI, -0.15 to 0.05; P<0.0001 for noninferiority) *Insulin glargine 300 u/mL was non-inferior to insulin degludec 100 u/mL*
Wysham, et al[26] (SWITCH-2) DB, MC, TTT, RCT, CO, Phase 3a	Insulin degludec (D) Vs. Insulin glargine (G) 16 week titration period and 16 week maintenance period	Adult patients with T2DM and at least 1 hypoglycemia risk factor and prior history of basal insulin use (with or without oral antidiabetic agents) (n=721)	Rate of overall symptomatic hypoglycemia rates[+] during maintenance period	D: 185.6/100 patient years G: 265.4/100 patient years RR 0.70 (95% CI, 0.61 to 0.80: P<0.001)

Key: * In combination with insulin degludec, + severe or blood glucose confirmed <56 mg/dL

Abbreviations: AC = active-controlled; CO = cross over; CSQI = continuous subcutaneous infusion; CV = cardiovascular; DB = double-blind; ED = event-driven; ETD = estimated treatment difference; HbA1c = hemoglobin A1c; LSMD = least square mean difference; MC = multi-center; MI = myocardial infarction; NI = non-inferiority; OL = open-label; PG = parallel group; RCT = randomized clinical trial; RR = rate-ratio; TTT = treat to target; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; u=units

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
insulin aspart	NOVOLOG	CARTRIDGE	SQ	Y
insulin aspart	NOVOLOG FLEXPEN	INSULN PEN	SQ	Y
insulin aspart	NOVOLOG	VIAL	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	VIAL	SQ	Y
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	SQ	Y
insulin lispro	HUMALOG	VIAL	SQ	Y
insulin lispro	INSULIN LISPRO	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	VIAL	SQ	Y
insulin NPH human isophane	HUMULIN N	VIAL	SQ	Y
insulin NPH human isophane	NOVOLIN N	VIAL	SQ	Y
insulin regular, human	HUMULIN R	VIAL	IJ	Y
insulin regular, human	NOVOLIN R	VIAL	IJ	Y
insulin regular, human	HUMULIN R U-500	VIAL	SQ	Y
insulin aspart (niacinamide)	FIASP FLEXTOUCH	INSULN PEN	SQ	N
insulin aspart (niacinamide)	FIASP	VIAL	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	SQ	N
insulin degludec	TRESIBA	VIAL	SQ	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	SQ	N
insulin detemir	LEVEMIR	VIAL	SQ	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	SQ	N
insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	SQ	N
insulin glulisine	APIDRA SOLOSTAR	INSULN PEN	SQ	N
insulin glulisine	APIDRA	VIAL	SQ	N
insulin lispro	HUMALOG	CARTRIDGE	SQ	N
insulin lispro	HUMALOG JUNIOR KWIKPEN	INS PEN HF	SQ	N
insulin lispro	ADMELOG SOLOSTAR	INSULN PEN	SQ	N

insulin lispro	HUMALOG KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-200	INSULN PEN	SQ	N
insulin lispro	INSULIN LISPRO KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	ADMELOG	VIAL	SQ	N
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	INSULN PEN	SQ	N
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	INSULN PEN	SQ	N
insulin NPH human isophane	HUMULIN N KWIKPEN	INSULN PEN	SQ	N
insulin regular, human	AFREZZA	CART INHAL	IH	N
insulin regular, human	HUMULIN R U-500 KWIKPEN	INSULN PEN	SQ	N

Appendix 2: Abstracts of Comparative Clinical Trials

A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5).

Klonoff DC, Evans ML, Lane W, Kempe HP, Renard E, DeVries JH, Graungaard T, Hyseni A, Gondolf T, Battelino T
AIM: To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) vs insulin aspart (IAsp) used in continuous subcutaneous insulin infusion (CSII) in participants with type 1 diabetes (T1D).
MATERIALS AND METHODS: This was a double-blind, treat-to-target, randomized, 16-week trial investigating CSII treatment with faster aspart (n = 236) or IAsp (n = 236). All available information, regardless of treatment discontinuation, was used for the evaluation of effect.
RESULTS: Faster aspart was non-inferior to IAsp regarding the change from baseline in glycated haemoglobin (HbA1c; primary endpoint). The mean HbA1c changed from 58.4 mmol/mol (7.5%) at baseline to 57.8 mmol/mol (7.4%) with faster aspart and to 56.8 mmol/mol (7.4%) with IAsp after 16 weeks' treatment, with an estimated treatment difference (ETD) of 1.0 mmol/mol (95% confidence interval [CI] 0.14; 1.87) or 0.09% (95% CI 0.01; 0.17; P < 0.001) for non-inferiority (0.4% margin; P < 0.02 for statistical significance in favour of IAsp). Faster aspart was superior to IAsp in change from baseline in 1-hour postprandial glucose (PPG) increment after a meal test (ETD -0.91 mmol/L [95% CI -1.43; -0.39] or -16.4 mg/dL [95% CI -25.7; -7.0]; P = 0.001), with statistically significant reductions also at 30 minutes and 2 hours. The improvement in PPG was reflected in the change from baseline in 1-hour interstitial glucose increment after all meals (ETD -0.21 mmol/L [95% CI -0.31; -0.11] or -3.77 mg/dL [95% CI -5.53; -2.01]). There was no statistically significant difference in the overall rate of severe or blood glucose-confirmed hypoglycaemia (estimated rate ratio 1.00 [95% CI 0.85; 1.16]). A numerical imbalance in severe hypoglycaemic episodes between faster aspart and IAsp was seen in the treatment (21 vs 7) and 4-week run-in periods (4 vs 0).
CONCLUSIONS**:** Faster aspart provides an effective and safe option for CSII treatment in T1D.

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes.

Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB
BACKGROUND: Degludec is an ultralong-acting, once-daily basal insulin that is approved for use in adults, adolescents, and children with diabetes. Previous open-label studies have shown lower day-to-day variability in the glucose-lowering effect and lower rates of hypoglycemia among patients who received degludec than among those who received basal insulin glargine. However, data are lacking on the cardiovascular safety of degludec.
METHODS: We randomly assigned 7637 patients with type 2 diabetes to receive either insulin degludec (3818 patients) or insulin glargine U100 (3819 patients) once daily between dinner and bedtime in a double-blind, treat-to-target, event-driven cardiovascular outcomes trial. The primary composite outcome in the

time-to-event analysis was the first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3. Adjudicated severe hypoglycemia, as defined by the American Diabetes Association, was the prespecified, multiplicity-adjusted secondary outcome.
RESULTS: Of the patients who underwent randomization, 6509 (85.2%) had established cardiovascular disease, chronic kidney disease, or both. At baseline, the mean age was 65.0 years, the mean duration of diabetes was 16.4 years, and the mean (±SD) glycated hemoglobin level was 8.4±1.7%; 83.9% of the patients were receiving insulin. The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06; P<0.001 for noninferiority). At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001). Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an absolute difference of 1.7 percentage points (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). Rates of adverse events did not differ between the two groups.
CONCLUSIONS: Among patients with type 2 diabetes at high risk for cardiovascular events, degludec was noninferior to glargine with respect to the incidence of major cardiovascular events. (Funded by Novo Nordisk and others; DEVOTE ClinicalTrials.gov number, NCT01959529 .).

A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study.

Ritzel R, Harris SB, Baron H, Florez H, Roussel R, Espinasse M, Muehlen-Bartmer I, Zhang N, Bertolini M, Brulle-Wohlhueter C, Munshi M, Bolli GB
OBJECTIVE: SENIOR compared the efficacy and safety of insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in older people (≥65 years old) with type 2 diabetes.
RESEARCH DESIGN AND METHODS: SENIOR was an open-label, two-arm, parallel-group, multicenter phase 3b trial designed to enroll ∼20% of participants aged ≥75 years. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to a fasting self-monitored plasma glucose of 5.0-7.2 mmol/L (90-130 mg/dL).
RESULTS: In total, 1,014 participants were randomized (mean age: 71 years). Comparable reductions in HbA_{1c} were observed from baseline to week 26 for Gla-300 (-0.89%) and Gla-100 (-0.91%) in the overall population (least squares mean difference: 0.02% [95% CI -0.092 to 0.129]) and for participants aged ≥75 years (-0.11% [-0.330 to 0.106]). Incidence and rates of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia events were low and similar between both treatment groups, with lower rates of documented symptomatic hypoglycemia with Gla-300. The lower risk of hypoglycemia with Gla-300 versus Gla-100 was more apparent in the subgroup aged ≥75 years versus the overall population. Significantly lower annualized rates of documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) hypoglycemia were observed (Gla-300: 1.12; Gla-100: 2.71; rate ratio: 0.45 [95% CI 0.25-0.83]).
CONCLUSIONS: Efficacy and safety of Gla-300 was demonstrated in older people (≥65 years of age) with type 2 diabetes, with comparable reductions in HbA_{1c} and similarly low or lower risk of documented symptomatic hypoglycemia versus Gla-100. A significant benefit in hypoglycemia reduction was seen in participants aged ≥75 years.

More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial.

Rosenstock J, Cheng A, Ritzel R, Bosnyak Z, Devisme C, Cali AMG, Sieber J, Stella P, Wang X, Frías JP, Roussel R, Bolli GB
OBJECTIVE: To compare insulin glargine 300 units/mL (Gla-300) versus insulin degludec 100 units/mL (IDeg-100) in this first head-to-head randomized controlled trial.

RESEARCH DESIGN AND METHODS: BRIGHT (NCT02738151) was a multicenter, open-label, active-controlled, two-arm, parallel-group, 24-week, noninferiority study in insulin-naive patients with uncontrolled type 2 diabetes. Participants were randomized 1:1 to evening dosing with Gla-300 (N = 466) or IDeg-100 (N = 463), titrated to fasting self-monitored plasma glucose of 80-100 mg/dL. The primary end point was HbA_{1c}change from baseline to week 24. Safety end points included incidence and event rates of hypoglycemia.
RESULTS: At week 24, HbA_{1c} improved similarly from baseline values of 8.7% (72 mmol/mol) in the Gla-300 group and 8.6% (70 mmol/mol) in the IDeg-100 group to 7.0% (53 mmol/mol)-least squares mean difference -0.05% (95% CI -0.15 to 0.05) (-0.6 mmol/mol [-1.7 to 0.6])-demonstrating noninferiority of Gla-300 versus IDeg-100 (P < 0.0001). Hypoglycemia incidence and event rates over 24 weeks were comparable with both insulins, whereas during the active titration period (0-12 weeks) the incidence and rate of anytime (24-h) confirmed hypoglycemia (≤70 and <54 mg/dL) were lower with Gla-300. Both insulins were properly titrated and exhibited no specific safety concerns.
CONCLUSIONS: Gla-300 and IDeg-100 provided similar glycemic control improvements with relatively low hypoglycemia risk. Hypoglycemia incidence and rates were comparable with both insulins during the full study period but lower in favor of Gla-300 during the titration period. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations.

Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial.

Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, Kvist K, Norwood P
IMPORTANCE: Hypoglycemia, a serious risk for insulin-treated patients with type 2 diabetes, negatively affects glycemic control.
OBJECTIVE: To test whether treatment with basal insulin degludec is associated with a lower rate of hypoglycemia compared with insulin glargine U100 in patients with type 2 diabetes.
DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, treat-to-target crossover trial including two 32-week treatment periods, each with a 16-week titration period and a 16-week maintenance period. The trial was conducted at 152 US centers between January 2014 and December 2015 in 721 adults with type 2 diabetes and at least 1 hypoglycemia risk factor who were previously treated with basal insulin with or without oral antidiabetic drugs.
INTERVENTIONS: Patients were randomized 1:1 to receive once-daily insulin degludec followed by insulin glargine U100 (n = 361) or to receive insulin glargine U100 followed by insulin degludec (n = 360) and randomized 1:1 to morning or evening dosing within each treatment sequence.
MAIN OUTCOMES AND MEASURES: The primary end point was the rate of overall symptomatic hypoglycemic episodes (severe or blood glucose confirmed [<56 mg/dL]) during the maintenance period. Secondary end points were the rate of nocturnal symptomatic hypoglycemic episodes (severe or blood glucose confirmed, occurring between 12:01 am and 5:59 am) and the proportion of patients with severe hypoglycemia during the maintenance period.
RESULTS: Of the 721 patients randomized (mean [SD] age, 61.4 [10.5] years; 53.1% male), 580 (80.4%) completed the trial. During the maintenance period, the rates of overall symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were 185.6 vs 265.4 episodes per 100 patient-years of exposure (PYE) (rate ratio = 0.70 [95% CI, 0.61-0.80]; P < .001; difference, -23.66 episodes/100 PYE [95% CI, -33.98 to -13.33]), and the proportions of patients with hypoglycemic episodes were 22.5% vs 31.6% (difference, -9.1% [95% CI, -13.1% to -5.0%]). The rates of nocturnal symptomatic hypoglycemia with insulin degludec vs insulin glargine U100 were 55.2 vs 93.6 episodes/100 PYE (rate ratio = 0.58 [95% CI, 0.46-0.74]; P < .001; difference, -7.41 episodes/100 PYE [95% CI, -11.98 to -2.85]), and the proportions of patients with hypoglycemic episodes were 9.7% vs 14.7% (difference, -5.1% [95% CI, -8.1% to -2.0%]). The proportions of patients experiencing severe hypoglycemia during the maintenance period were 1.6% (95% CI, 0.6%-2.7%) for insulin degludec vs 2.4% (95% CI, 1.1%-3.7%) for insulin glargine U100 (McNemar P = .35; risk difference, -0.8% [95% CI, -2.2% to 0.5%]). Statistically significant reductions in overall and nocturnal symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were also seen for the full treatment period.

CONCLUSIONS AND RELEVANCE: Among patients with type 2 diabetes treated with insulin and with at least 1 hypoglycemia risk factor, 32 weeks' treatment with insulin degludec vs insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemia.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 5 2019

Search Strategy:

#	Searches	Results
1	inulin glargine.mp.	0
2	insulin determir.mp.	2
3	insulin aspart.mp. or Insulin Aspart/	902
4	insulin NPH.mp. or Insulin, Isophane/	1067
5	insulin lispro.mp. or Insulin Lispro/	1047
6	insulin regular.mp. or Insulin/	179973
7	insulin degludec.mp.	322
8	insulin glulisine.mp.	205
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	180887
10	limit 9 to (english language and humans and yr="2017 -Current")	5553
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	233

Appendix 4: Key Inclusion Criteria

Population	Patients with type 1 and type 2 diabetes
Intervention	Insulins
Comparator	Other active treatments or placebo
Outcomes	Mortality, micro and macrovascular complications, glucose lowering, hypoglycemia
Timing	New onset or established diabetes
Setting	Outpatient

Insulins

Goal:

- Restrict certain insulin products to specific patient populations to ensure appropriate use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred insulin vials
- All pre-filled insulin pens, cartridges and syringes with the exception of insulin glargine (Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the request for an insulin pen or cartridge?	**Yes:** Go to #4	**No:** Go to #7
4. Is the request for either a short-acting or a long-acting insulin pen or cartridge?	**Yes:** Go to #5	**No:** Got to #6
5. Has the patient tried and failed or have contraindications to either: • insulin aspart (Novolog®) if the request is for short-acting insulin OR • insulin glargine (Lantus®) if the request is for long-acting insulin?	**Yes:** Go to #6	**No:** Pass to RPh; deny and recommend a trial of insulin glargine (Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)

Approval Criteria		
6. Will the insulin be administered by the patient or a non-professional caregiver **AND** do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is a child less than 18 years of age?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness
7. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Approve for up to 12 months

P&T / DUR Review: *9/19 (KS); 11/18 (KS); 9/17; 3/16; 11/15; 9/10*
Implementation: *11/1/17; 10/13/16; 1/1/11*

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Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: July 2019

Date of Last Review: November 2017
Dates of Literature Search: April 2019
Brand Name (Manufacturer): Spravato™ (Janssen)
Zulresso™ (Sage)
Dossiers Received: yes

Generic Name: esketamine
Generic Name: brexanolone

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
This class update is primarily in response to the approval of two new antidepressants: esketamine (Spravato™) and brexanolone (Zulresso™). New high quality comparative efficacy and safety evidence on antidepressants published since the last update, presented in 2017, will also be evaluated and included.

Research Questions:
1. Is there new high-quality evidence demonstrating differences in efficacy or effectiveness between the different antidepressants or classes of antidepressants for major depressive disorder (MDD), generalized anxiety disorder (GAD) or other conditions?
2. Is there evidence demonstrating differences in harms data between the different antidepressants?
3. Are there subgroups of patients, based on demographics (e.g., age, race, sex, socio-economic factors), in which one antidepressant medication would be more effective or associated with less harm?
4. What is the evidence for efficacy and harms associated with esketamine and how does this compare to other antidepressants?
5. What is the evidence for efficacy and harms associated with brexanolone and how does this compare to other antidepressants?

Conclusions:
Depression
- Guidelines by the National Institute of Health and Care Excellence (NICE) recommend fluoxetine first-line in children and young people who require treatment with an antidepressant.[1]

Anxiety
- There is moderate strength of evidence that the treatment of children with imipramine or sertraline improve primary anxiety symptoms (which was considered a large treatment effect as assessed by standardized measurement) based on two good quality systematic reviews.[2,3]

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- An Agency for Healthcare Research and Quality (AHRQ) systematic review found moderate to high strength of evidence that serotonin-norepinephrine uptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) were effective in reducing the symptoms of anxiety in children, which was considered a moderate and large treatment effect, respectively.[3]
- Moderate quality evidence found a reduction in relapse for SSRIs, compared to placebo, in the treatment of social anxiety disorder as described in a 2017 Cochrane Systematic Review.[4] SNRIs were associated with a larger decrease in anxiety symptom scores compared to placebo, in this same population.[4]

Posttraumatic Stress Disorder

- An AHRQ review found moderate strength of evidence that fluoxetine, paroxetine, and venlafaxine are effective for reducing symptoms of posttraumatic stress disorder (PTSD) in adult patients.[5] Use of SSRIs and the SNRI, venlafaxine, for PTSD are also supported by NICE guidelines.[6]

Esketamine (Spravato)

- Esketamine nasal spray is indicated for treatment resistant depression and was found to be more effective than placebo in improving Montgomery-Asberg Depression Rating Scale (MADRS) scores with a mean difference of -4 points (95%CI, -7.3 to -0.64; P=0.020) at day 28 in patients with treatment resistant depression (TRD) that were also taking oral antidepressants.[7] Results were considered clinically significant, as demonstrated by a MADRS score change of 2 or more points. Two other trials did not demonstrate superiority of esketamine compared to placebo, in part due to a higher withdrawal rate in the high-dose group of esketamine patients, lower overall effect size than assumed in the protocol, and higher placebo response than anticipated.[7,8]
- Esketamine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program, which includes receiving esketamine in a REMS certified healthcare setting and monitoring patients for two hours after administration. Esketamine has a boxed warning due to sedation, dissociation, abuse and misuse and increased suicidal thoughts and behaviors in pediatric patients and adolescents taking antidepressants. Dissociation was experienced in 41% of patients, nausea in 28%, dizziness in 29%, and sedation in 23%.[9]

Brexanolone (Zulresso)

- Intravenous (IV) brexanolone was more effective than placebo in reducing Hamilton Rating Scale for Depression (HAM-D) scores in women with post-partum depression (PPD) by a mean difference reduction ranging from -2.5 to -5.5 points ($p<0.05$).[10] Reduction in HAM-D scores are clinically meaningful for reductions of 3-7 points, indicating borderline clinically significant benefits of brexanolone compared to placebo. Results for the secondary outcome, Clinical Global Impression-Improvement (CGI-I) responders, was higher in patients randomized to brexanolone compared to placebo (number needed to treat [NNT] of 3-4).
- Brexanolone has a boxed warning for excessive sedation or sudden loss of consciousness requiring continuous pulse oximetry monitoring. Brexanolone is only available through a REMS program.[11]

Safety

- A high quality review from AHRQ found an increased risk of adverse events in the acute phase of treatment in older patients (65 years or older) treated with duloxetine and venlafaxine compared to placebo, with a number needed to harm (NNH) of 10 (high strength of evidence).[12] In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (relative risk [RR] 1.85; 95% CI, 1.05 to 3.27; NNH 17).[12] Vortioxetine was associated with less adverse events compared to duloxetine based on high strength of evidence (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12] High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of clinical efficacy.
- Recommend prior authorization criteria for brexanolone and esketamine based on safety concerns.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics and cost.
- There were no policy changes based on efficacy or safety evidence presented in the last review.
- Anti-depressants are designated preferred or part of the voluntary PDL.

Background:

Antidepressants are most commonly used for MDD but have demonstrated efficacy in many other disorders, including: obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorders and pain syndromes.[13] The therapeutic effect of antidepressants is to target serotonin, dopamine and norepinephrine levels.

Major depressive disorder is defined as a chronic disorder in patients experiencing depressed mood or diminished interest or pleasure in activities of daily living. Symptoms of depression are weight changes, changes in appetite and/or sleep, fatigue, feelings of worthlessness, inability to concentrate and feelings of death or suicide that last at least 2 weeks.[13] The cause of depression is usually a combination of internal, external and traumatic factors that coincide to precipitate MDD. The incidence of MDD has steadily increased with the lifetime incidence in the United States of 17%.[14] Females have almost twice the risk as males for the development of depression. MDD has been associated with the second leading cause of disability.

Antidepressants, in combination with cognitive behavioral therapy, are the main treatment modalities for the treatment of MDD.[13] Antidepressants are divided into first- and second-generation treatments. First-generation classes are tricyclics and monoamine oxidase inhibitors. Second generation antidepressants include SSRIs, SNRIs, atypicals, and serotonin modulators. The SSRIs increase serotonin and are recommended as first-line agents due to efficacy and tolerability. Commonly used second-line therapies include SNRIs and serotonin modulators.[13] There is no evidence of clinically meaningful differences in efficacy between the different antidepressants. Adverse effects, safety, comorbidities, drug interactions and cost are common determining characteristics in choosing antidepressant therapy.

Effectiveness of antidepressant treatment is based on symptom improvement, function, and quality of life. Treatment response is measured by a provider administered depression rating scale. Response is considered improvement of 50% or more but less than the threshold for remission. Remission is defined as a score less than or equal to a predefined "normal range" for that scale. Commonly used symptom scales are presented in **Table 1**.

Table 1. Depression Symptom Patient Assessment Tools

Assessment	Description	Remission Score	Clinically Meaningful Important Difference
Hamilton Rating Scale for Depression (HAM-D)[15,16]	17 items, each item has a range of 0-2	Less than or equal to 7	3 to 7

Montgomery-Asberg Depression Rating Scale (MADRS)[17]	10 items, clinician-rate scale, range of 0-60, higher scores indicate a higher severity of depression	MADRS total score of less than or equal to 12 for at least 3 of the last 4 weeks	1.6 to 1.9
Patient Health Questionnaire -9 item (PHQ-9)[18]	Nine items with a score of 0-27 based on a 4-point Likert score for each item	Less than 5	Treatment score of less than 9 and 50% improvement in symptoms
Clinical Global Impression-Improvement Score (CGI-I)[19]	7-point scale in which illness is documented as improved or worsened – higher scores represent worsening symptoms/functioning	Response defined as 1 (very much improved) or 2 (much improved)	Not described

Approximately 130,000 fee-for-service (FFS) patients had a diagnosis of MDD in the last year. Antidepressant therapy accounts for a large portion of the Oregon Health Authority (OHP) drug benefit budget. Medications in this class are preferred or on a voluntary PDL. In the last quarter, 64% of the antidepressant claims were for preferred therapies.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Depression

AHRQ- Adverse Effects of Pharmacological Treatments of Major Depression in Older Adults

A systematic review and meta-analysis was done by AHRQ to study the adverse effects of pharmacological treatments for MDD in adults, 65 years and older.[12] Classes of antidepressants included in the review are SSRIs, SNRIs and others (bupropion, mirtazapine, trazodone, vilazodone and vortioxetine). Specific outcomes of interest were: any adverse event, bleeding, blood pressure changes, cognitive measures and electrocardiogram changes, emergency department (ED) visits, falls, fractures, hospitalizations, mortality, seizures, suicidal thoughts/attempts, syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia, weight changes or withdrawals due to adverse events. Thirty-nine publications were included in the review, 37 were randomized controlled trials and two were observational studies. In general, evidence of clinical efficacy in patients 65 years and older is of low quality; however, SSRIs and bupropion XR are most commonly used.[12] Outcomes with moderate to high strength of evidence will be presented.

SSRIs versus Placebo or No Treatment

- There was moderate strength of evidence of no difference in adverse events in the acute phase between SSRIs (fluoxetine and escitalopram) and placebo or no treatment and the strength of evidence for all other outcome comparisons were of low or insufficient quality.[12]

SSRIs versus Tricyclic Antidepressants

- Three trials were identified comparing SSRIs versus TCAs; however, all findings were of low strength of evidence or insufficient findings.[12]

SSRIs versus SSRIs

- A comparison between sertraline and fluoxetine and a comparison between escitalopram and fluoxetine found moderate strength of evidence of no difference in the incidence of any adverse events in the acute phase.
- No difference in any adverse events or serious adverse events in the maintenance phase was found in a comparison between paroxetine and fluoxetine based on moderate evidence.[12]

SNRIs versus Placebo

- In the acute phase of treatment there was high strength of evidence of increased risk of adverse events with duloxetine and venlafaxine compared to placebo with a NNH of 10.[12]
- In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (RR 1.85; 95% CI, 1.05 to 3.27; NNH 17).[12]
- The risk of withdrawals due to adverse events was higher with duloxetine compared to placebo in the acute and continuation phase of treatment based on moderate strength of evidence with a NNH of 12 (RR 2.64; 95% CI, 1.21 to 5.73).[12]
- An increased risk of falls during the acute and maintenance phase was found with duloxetine versus placebo based on moderate strength of evidence (RR 1.69; 95% CI, 1.03 to 2.76; NNH 10).[12]
- There was moderate strength of evidence of no difference between duloxetine and placebo for the outcomes of ECG-QTc changes and serious adverse events in the acute and continuation phase.
- Serum sodium and body weight were reduced in the acute phase of MDD treatment in patients taking duloxetine compared to placebo (specific results not available).

SNRIs versus SSRIs

- There was no difference between the comparison of venlafaxine and citalopram for the outcomes of any adverse events, serious adverse events, or withdrawals due to adverse events in the continuation phase based on moderate evidence.[12]
- There was moderate strength of evidence of no difference between venlafaxine and fluoxetine for any adverse events in the acute phase.

Bupropion XR versus Placebo

- There was no evidence of differences between bupropion XR and placebo for the outcome of any adverse event based on moderate strength of evidence.[12]

Mirtazapine versus Paroxetine

- Moderate evidence found no difference in any adverse events in the acute treatment phase between mirtazapine and paroxetine.

Trazodone versus No Antidepressant Use

- All outcomes were of low strength of evidence.[12]

Vortioxetine

- There was no difference between vortioxetine compared to placebo for the outcomes of any adverse events and serious adverse events, in the acute phase, based on high and moderate strength of evidence, respectively.

- No difference in serious adverse events and withdrawals due to adverse events in the acute phase were found between vortioxetine versus duloxetine based on moderate evidence.
- High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12]

Limitations to the review are that none of the randomized controlled trials included in the review were specifically designed to study adverse events and, therefore, resulted in findings of low or insufficient evidence in some comparisons.

Cochrane – Antidepressants for Treating Depression in Dementia

A 2018 systematic review and meta-analysis done by Cochrane analyzed the efficacy and safety of antidepressant therapy in patients with a diagnosis of dementia and coexisting depression.[20] A literature search up until August of 2018 identified ten randomized controlled trials which were included in the qualitative synthesis. Eight trials were identified for the meta-analysis. The mean age of included participants was 80 years old and mean dementia severity was 19.65, as determined by the mean Mini Mental State Examination (MMSE) score, which is considered mild dementia.[20] Drug classes included in the study where tricyclic antidepressants (TCA), SSRIs, SSRI/SNRIs and one study evaluated a reversible monoamine oxidase inhibitor. All but two studies had unclear risk of bias. The primary outcome was the effect on depression (as determined by a response and remission based on rating scales). Other important outcomes include the number of patients with remission, effect on cognitive function, activities of daily living impact, adverse events and withdrawals.[20]

There was high quality evidence demonstrating no evidence of effectiveness for patients with dementia treated with antidepressants, compared to placebo, based on depression endpoint score ratings at 6 to 13 weeks (standard mean difference [SMD] -0.10 (95% CI, -0.26 to 0.06).[20] A subgroup analysis of only SSRIs found little or no difference of efficacy, based on score ratings, compared to placebo. The number of patients with remission at 6 to 12 weeks was found to be higher in patients with dementia treated with antidepressants compared to placebo, 217/1000 versus 415/1000 (OR 2.57; 95% CI, 1.44 to 4.59) based on moderate quality evidence.[20] Changes based on responder rates were considered low quality evidence and therefore not included. There was moderate quality evidence that antidepressant therapy was associated with more drop outs compared to placebo. Patients taking antidepressants were more likely to experience an adverse event compared to placebo based on moderate quality evidence. In summary, there is no strong evidence for the treatment of depression in patients with dementia.

Cochrane – Antidepressants for the Treatment of People with Co-occurring Depression and Alcohol Dependence

A 2018 Cochrane review was done to determine the efficacy and harms of antidepressant use in patients with alcohol dependence.[21] There were 33 randomized controlled trials that met inclusion criteria, 18 of the trials were conducted in an outpatient setting. Included patients were a mean age of 42 years and 68% were men. Trials ranged from 3 to 26 weeks and included placebo, psychotherapy and other medications (including other antidepressants).[21] Medications included in the review were amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, nefazodone, paroxetine, and venlafaxine. The primary outcome was the full remission of depression.

There was no difference found in the rate of full remission of depression in antidepressant versus placebo comparisons; however, there were only 4 included studies and there was a high degree of heterogeneity (I^2=66%).[21] There was moderate quality of evidence that the number of patients that were abstinent from alcohol were higher in the antidepressant group compared to placebo with RR of 1.71 (95% CI, 1.22 to 2.39; p=0.002).[21] In addition, the mean number of alcoholic drinks per day was lower in patient taking antidepressants compared to placebo by 1.13 drinks per drinking days (95% CI, 1.79 to 0.46).[21] All other studied outcomes were of very low or low quality evidence.

Limitations include a small number of include trials for comparison and one-third of studies were completed in countries outside the US. Overall, there is limited evidence of efficacy of antidepressants for the treatment of patients with co-occurring depression and alcohol dependence.

Anxiety

Cochrane – Pharmacotherapy for Social Anxiety Disorder (SAnD)

A 2017 Cochrane review evaluated treatments used for SAnD in adult patients.[4] Sixty-six trials met inclusion criteria for the review and approximately half were testing the efficacy of SSRIs. The average trial size was small with the average number of trial participants being 176, and all trials had durations of 24 weeks or less. The primary outcome was treatment response (assessed by CGI-I). Important secondary outcomes were SAnD symptom severity (assessed by the Liebowitz Social Anxiety Scale [LSAS]) and rate of relapse. The CGI-I ranges from 1-7 with higher numbers indicating very ill patients. A change of 1 represents (very much) improved and a change of 2 as (improved). The LSAS is a 24-item scale with higher scores representing a higher level of social anxiety (>95 indicating very severe social phobia).

Clinician rated LSAS total score demonstrated a reduction of anxiety symptoms by 11.91 points (95% CI −16.06 to −7.76; $p<0.05$) lower in the SNRI group compared to placebo, in patients with low to moderate social phobias. In patients that took SSRIs (paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram), there was moderate evidence of a reduced rate of relapse compared to placebo with a RR of 0.34 (95% CI, 0.22 to 0.5; $p<0.00001$).[4] In an overall comparison across all medication classes, there was evidence of higher efficacy with treatment compared to placebo; however, this analysis was associated with a high degree of heterogeneity ($I^2=69.7\%$).[4]

AHRQ – Anxiety in Children

An AHRQ review evaluated efficacy and harms of therapies for childhood anxiety disorders (e.g., panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder and separation anxiety).[3] A total of 206 studies compared psychotherapy, pharmacotherapy, or combination of treatments in children from the ages of 3 to 18 years. Primary anxiety symptoms were the primary outcome of interest.

In summary, SSRIs (fluoxetine, paroxetine, and sertraline) and SNRIs (atomoxetine, duloxetine and venlafaxine) improved primary anxiety symptoms compared to placebo based on moderate to high evidence.[3] SSRIs also demonstrated efficacy in improved remission rates, function, and clinical response compared to placebo (moderate to high strength of evidence). TCAs and benzodiazepines lacked conclusive evidence of benefit. Specific results for comparisons with moderate or high strength of evidence are presented in **Table 2**. Limitations to the data include small number of studies available for the analysis, small sample sizes, and imprecision in the data.

Table 2. Results for Evidence in the Treatment of Children with Anxiety[3]

Comparison	Outcome	Results*	Strength of Evidence
Drugs +/- Cognitive Behavioral Therapy [CBT] versus CBT			
Imipramine and CBT Vs. CBT	Primary anxiety/patient reported	SMD: -0.74 (95% CI, -1.26 to -0.23) *Imipramine and CBT reduced anxiety more than CBT alone*	Moderate
	Function	SMD: -1.27 (95% CI, -1.81 to -0.73) *Imipramine and CBT improved function more than CBT alone*	Moderate

CBT and sertraline Vs. CBT	Primary anxiety/clinician reported	SMD: -0.69 (95% CI, -0.93 to -0.45) *Sertraline and CBT reduced anxiety more than CBT alone*	Moderate
	Function	SMD: -0.47 (95% CI, -0.70 to -0.23) *Sertraline and CBT improved function more than CBT alone*	Moderate
Fluoxetine Vs. CBT	Primary anxiety/clinician reported	SMD: 0.78 (95% CI, 0.37 to 1.18) *Increased anxiety with fluoxetine*	Moderate
	Function	SMD: 0.54 (95% CI, 0.14 to 0.94) *Fluoxetine reduced function*	Moderate
Sertraline Vs. CBT	Remission	RR 1.51 (95% CI, 1.22 to 1.86) *Sertraline improved remission more than CBT*	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) *Sertraline improved response more than CBT*	Moderate
CBT and sertraline Vs. Sertraline	Primary anxiety/clinician report	SMD: -0.46 (95% CI, -0.70 to -0.22) *CBT and sertraline reduced anxiety more than sertraline alone*	Moderate
	Function	SMD: -0.34 (95% CI, -0.58 to -0.10) *CBT and sertraline improved function more than sertraline alone*	Moderate
	Remission	RR 1.51 (95% CI, 1.22 to 1.87) *CBT and sertraline improved remission rates more than sertraline alone*	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) *CBT and sertraline improved responses more than sertraline alone*	Moderate
Drugs versus Placebo			
SNRI Vs. Placebo	Primary anxiety/clinician report	SMD: -0.45 (95% CI, -0.81 to -0.10) *SNRIs reduced anxiety more than placebo*	High
SSRI Vs. Placebo	Primary anxiety/parent report	SMD: -0.61 (95% CI, -1.03 to -0.20) *SSRIs reduced anxiety more than placebo*	Moderate
	Primary anxiety/clinician report	SMD: -0.65 (95% CI, -1.10 to -0.21) *SSRIs reduced anxiety more than placebo*	Moderate
	Function	SMD: -0.59 (95% CI, -0.85 to -0.34) *SSRIs improved function more than placebo*	High
	Remission	RR 2.04 (95% CI, 1.37 to 3.04) *SSRIs improved remission rates more than placebo*	Moderate
	Response	RR 1.96 (95% CI, 1.60 to 2.40) *SSRIs improved response rates more than placebo*	Moderate

Key: * SMD cutoffs of 0.20, 0.50, and 0.80 are considered to represent small, moderate, and large effect, respectively.

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval; SMD = standard mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Cochrane – Antidepressants versus Placebo for Panic Disorder in Adults

The efficacy and harms of antidepressants for the treatment of panic disorder in adults was the topic of a recent Cochrane systematic review.[22] Forty-one randomized, placebo-controlled trials were included with study durations of 8 to 28 weeks. Classes of drugs that were included in the review were: TCAs (17 studies), SSRIs (22 studies), SNRIs (4 studies), MAOIs (1 study), norepinephrine reuptake inhibitor (NRI) (1 study – reboxetine, which is not available in the US). Two studies had active treatment comparisons (nefazodone and ritanserin). Most studies had an unclear risk of selection and performance bias.

There was moderate quality evidence demonstrating less dropouts in patients taking antidepressants compared to placebo with a mean difference of 38 fewer dropout per 1000 patients (RR 0.88; 95% CI, 0.81 to 0.97; number needed to benefit [NNTB] 27).[22] The benefit was driven by TCAs, as there was no difference from placebo for SSRIs and SNRIs. Risk associated with failure to obtain remission was lower with antidepressant treatment compared to placebo based on moderate evidence (RR 0.83; 95% CI, 0.78 to 0.88), and a mean difference of 101 patients per 1000 treated fewer patients failed to remit in the antidepressant group.[22] There was an increased risk of dropouts due to adverse events in the antidepressant group compared to placebo with a RR of 1.49 (95% CI, 1.25 to 1.78), based on moderate evidence.[22] This was most common with TCAs and SSRIs.

Limitations to this review include unclear risk of bias in some domains and insufficient long-term data. Overall, there is not robust evidence to support the treatment of panic disorder in adults with antidepressants.

Wang, et al. – Comparative Effectiveness and Safety of Cognitive Behavioral Therapy and Pharmacotherapy for Childhood Anxiety Disorders

A recent good quality systematic review and meta-analysis included 7719 children and adolescents (mean age of 9 and 56% female) with a diagnosis of panic disorder (31%), social anxiety disorder (71%), specific phobias, generalized anxiety disorder (63%) or separation anxiety (61%) that were receiving cognitive behavioral therapy (CBT), pharmacotherapy or both.[2] Patients who were using pharmacotherapy were on SSRIs, SNRIs, tricyclic antidepressants (TCAs), and benzodiazepines. Most studies were up to 12 weeks in duration with the longest study lasting 32 weeks. The overall risk of bias was considered moderate to high due to lack of blinding of patients, providers, and outcome assessors, in addition to an unclear risk of conflicts of interest. Determination of publication bias, related to pharmacotherapy, was not done due to lack of studies. The primary outcome of the review was the occurrence of primary anxiety symptoms (as measured by a standardized measure of child anxiety symptoms), clinical remission, treatment response and adverse events.[2]

There was moderate quality of evidence that SSRIs were more effective at reducing anxiety symptoms compared to placebo, as reported by parents (SMD -0.61; 95% CI, -1.03 to -0.20) and clinicians (SMD -0.65: 95% CI, -1.10 to -0.21).[2] There was high heterogeneity with both findings, ranging from 55% to 73%. SSRIs were also associated with higher remission rates compared to placebo (RR 2.04; 95% CI, 1.37 to 3.04) and response (RR 1.96; 95% CI, 1.60 to 2.40), both based on moderate quality of evidence.[2] The efficacy of SNRIs on primary anxiety symptom reduction, as reported by clinicians, was higher than placebo based on high quality of evidence and a standard mean difference of -0.45 (95% CI, -0.81 to -0.10).[2] Active treatment was more commonly associated with adverse events but none were considered serious.

CBT was more effective than wait listing/no treatment in reducing primary anxiety symptoms based on child, parent and clinician assessments, SMD -0.77, -0.88 and -1.38, respectively (moderate quality evidence).[2] Clinician-assessed treatment response was also improved based on moderate quality evidence (RR 4.72; 95% CI, 2.39 to 9.32).[2] All estimates had a high degree of heterogeneity. Moderate quality evidence found the combination therapy of imipramine and CBT, compared to CBT alone, reduced primary anxiety symptoms based on child assessment, SMD of -0.74 (95% CI, -1.26 to -0.23).[2] Sertraline combined with CBT reduced primary anxiety symptoms (SMD 0.69; 95% CI, -0.93 to -0.45), improved treatment response (RR 1.35; 95% CI, 1.15 to 1.58), and remission (RR 1.51; 95% CI, 1.22 to 1.86) when compared to CBT alone based on clinician assessment.[2] In a comparison of sertraline to CBT, there was no difference in the reduction of primary anxiety

symptoms. There was moderate quality evidence that CBT was more effective than fluoxetine at reducing primary anxiety symptoms based on clinician assessment (SMD -0.78; 95% CI, -1.18 to -0.37).[2]

Posttraumatic Stress Disorder

AHRQ- Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder

A systematic review and meta-analysis was done by AHRQ to evaluate the efficacy and harms of treatments for PTSD.[5] This 2018 report updates a previous 2013 version. The report analyzes the psychological as well as pharmacotherapy recommendations; however, the focus of this summary will be on the evidence for medications which included the following classes: SSRIs, SNRIs, TCAs, and other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone). Paroxetine and sertraline are the only therapies approved for the treatment of PTSD; however, the other therapies are often used off-label for the treatment of PTSD. Patients 18 years old and older with PTSD (diagnosed by any DSM criteria) were included.[5] The primary outcome was the reduction in PTSD symptoms.

There was moderate quality of evidence that treatment with fluoxetine, paroxetine and venlafaxine were more effective than placebo (**Table 3**).[5] All studies of fluoxetine, paroxetine and venlafaxine demonstrated medium risk of bias. Overall, SSRIs were associated with a reduction in clinician administered PTSD symptom scores, with a SMD of -0.30 (95% CI, -0.40 to -0.20; p=0.041).[5] Depression symptoms were reduced with SSRIs compared to placebo in patients with PTSD by a SMD of -0.24 (95% CI, -0.38 to -0.11; p<0.001).[5] Two trials provided direct evidence comparisons; venlafaxine extended release (ER) versus sertraline and paroxetine + placebo versus desipramine + placebo. Both trials found similar decreases in PTSD symptoms; however, comparisons were considered insufficient or low strength of evidence. A head to head comparison of venlafaxine ER to sertraline found moderate strength of evidence of no difference for changes in depression symptoms.

Table 3. Outcomes for Pharmacological Treatment used in PTSD with Moderate to High Strength of Evidence (placebo comparisons)[5]

Treatment	Outcome	Result	Interpretation	Strength of Evidence
Fluoxetine	PTSD symptoms	SMD -0.28 (95% CI, -0.42 to -0.14)	Fluoxetine reduced PTSD symptoms	Moderate
Paroxetine	PTSD symptoms	SMD -0.44 to -0.56 (CI not provided)	Paroxetine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD 0.13 to 0.19 (CI not provided)	Paroxetine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -0.60 to -0.34 (CI not provided)	Paroxetine reduced depression symptoms	Moderate
Venlafaxine	PTSD symptoms	SMD -0.35 to -0.26 (CI not provided)	Venlafaxine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD of 0.12 to 0.15 (CI not provided)	Venlafaxine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -2.6 to -1.6 (CI not provided)	Venlafaxine was associated with reduced depression symptoms	Moderate
Abbreviations: CI = confidence interval; PTSD =posttraumatic stress disorder; RD =risk difference; SMD = standardized mean difference				

Direct comparative effectiveness evidence was insufficient for most pharmacotherapy comparisons for PTSD and for commonly used treatments such as escitalopram, fluvoxamine, desvenlafaxine, duloxetine, TCAs and other second-generation antidepressants.

After review, 22 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

NICE – Depression in Adults: Recognition and Management

A 2009 review that was updated in April 2018 provided guidance for adults who present with depression as the primary diagnosis.[16] If antidepressants are indicated, a choice should be made based on adverse events, drug interactions, patient comorbidities and perception and tolerability of previous treatments. Recommendations:

- Generic SSRIs are recommended first-line based on efficacy and tolerability.
    - SSRIs have an increased risk of bleeding and caution is advised in older patients or in patients taking other medications that are known to damage the mucosa of the gastrointestinal tract or interfere with clotting.
    - Drug interactions are most common with fluoxetine, fluvoxamine, and paroxetine.
    - Paroxetine is associated with a high risk of discontinuation.
- For patients at increased risk of suicide:
    - Venlafaxine is associated with a higher risk of death due to overdose than other equally effective antidepressants used for routine use in primary care.
    - TCAs are associated with the greatest risk of overdose.
- The following considerations are warranted with antidepressant use other than SSRIs
    - Higher discontinuation rates with TCAs
    - Some antidepressants may require monitoring, have specific cautions or contraindications which need to be considered with each individual patient.
- If symptoms have not improved in 3-4 weeks of antidepressant therapy consider increasing the antidepressant dose or switching to another antidepressant.

NICE – Post-traumatic Stress Disorder

NICE updated their guidance on post-traumatic stress disorder in 2018. Medication therapy is not recommended for prevention of PTSD.[6] If medication is appropriate for treatment, venlafaxine or a SSRI (e.g., sertraline) is recommended for adult patients. Treatment effectiveness should be assessed frequently and monitored for adverse reactions. Antipsychotics, such as risperidone, should be considered only with the following qualifying factors: presence of disabling symptoms and behaviors (e.g., severe hyperarousal or psychotic symptoms) and when symptoms have not responded to other drug or psychological treatments.

NICE – Depression in Children and Young People: Identification and Management

The treatment of depression in children and young people was the focus of a September 2017 update.[1] In patients with mild depression, antidepressant therapy is not recommended for initial treatment in children and young people. All antidepressant treatment should be offered in conjunction with psychotherapy and follow an assessment and diagnosis by a child and adolescent psychiatrist. In individuals with moderate to severe depression who continue to have symptoms despite the care of a multidisciplinary team, fluoxetine should be offered if patients are 12-18 years old. In younger children, ages 5 to 11, fluoxetine could be cautiously considered if they are unresponsive to psychological therapy (minimum of 4 sessions), although evidence is limited. Guidance for the use of antidepressants in children and young people is outlined in **Table 4**.[1] Venlafaxine, paroxetine and TCAs should not be used in children and young people for the treatment of depression.

Table 4. Recommendations for Medication Use in Children and Young Persons[1]

First-line Therapy - Fluoxetine
• Starting fluoxetine dose should be 10 mg daily • Fluoxetine dose can be increased to 20 mg daily after 1 week if clinically indicated • Medication should be continued for at least 6 months after remission
Second-line Therapies
• Sertraline or citalopram are the recommended second-line therapies • Medication should be continued for at least 6 months after remission • Starting dose should be half the adult dose • Dose can be titrated over the next 2 to 4 weeks up to the adult dose, if clinically indicated

US Preventative Services Task Force – Interventions to Prevent Perinatal Depression

A systematic review and meta-analysis was completed in 2019 to determine the benefits and harms of interventions offered in primary care to prevent perinatal depression (major or minor depressive episode during pregnancy or up to 1 year after childbirth).[23] Randomized and non-randomized controlled trials were included. Behavior-based interventions, antidepressants, and dietary supplements were studied for prevention in perinatal depression in pregnant and postpartum women or those at increased risk of perinatal depression. There was insufficient evidence to determine the benefits or harms of antidepressants in this population.

After review, four guidelines were excluded due to poor quality.[24–27]

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 155 citations were manually reviewed from the initial literature search. After further review, 154 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Jacobsen, et al[28] RCT, DB, MC	Vortioxetine Vs. Escitalopram (8 weeks)	Adults (40% male) with well-treated MDD experiencing treatment-emergent sexual dysfunction (n=447)	Change from baseline in the CSFQ-14 total score after 8 weeks	Vortioxetine: 8.8 Escitalopram: 6.6 MD: 2.2 (CI not provided) P = 0.013 *Vortioxetine improved sexual dysfunction scores more than escitalopram*
Key: CSFQ-14 – 14 item scale with 36 items with higher scores indicating higher sexual frequency[29] Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire Short Form; DB =double-blind; RCT-=randomized controlled trial				

NEW DRUG EVALUATION: Esketamine (Spravato™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Esketamine is a Schedule III nasal spray which is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for use in conjunction with oral antidepressants for the treatment of TRD in adults.[9] Esketamine should be administered under the supervision of a medical provider and is made available only through a restricted program called the Spravato REMS. The dose of esketamine ranges from 56-84 mg and is given twice weekly during the induction phase and once weekly during the maintenance phase (**Table 6**). Patient should be monitored for 2 hours after administration. Baseline blood pressure monitoring and blood pressure reassessment at 40 minutes post-dose, and subsequently if warranted, is recommended.[9]

Table. 6. Esketamine Intranasal Dosing Recommendations[9]

Phase	Dose
Induction Phase – weeks 1-4 Twice weekly dosing	56 mg for initial dose; subsequent doses are 56-84 mg. At the end of the induction phase, the maintenance phase dose should be continuation of the initial dose.
Maintenance Phase – weeks 5-8	56 or 84 mg once weekly
Maintenance Phase – week 9 and thereafter	56 or 84 mg once weekly or once every other week (i.e., every 2 weeks)
* Each device contains 28 mg of esketamine in two sprays; 2 devices for the 56 mg dose and 3 devices for the 84 mg dose	

Five, phase 3, randomized, placebo-controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUTSTAIN-2) were used to determine the clinically efficacy and safety of esketamine in adult patients with TRD. TRANSFORM-2 and SUSTAIN-1 are the only published study so the efficacy and safety results of the other trials will be based on data from prescribing information and the esketamine dossier.[7,8]

TRANSFORM-2 included patients (n=223), mean age of 47 years, with MDD (mean MADRS score of 37) who had not responded adequately to at least two different antidepressants appropriately titrated and treatment of adequate duration in the current depressive episode (**Table 9**).[7] All patients received open-label oral antidepressant therapy, 32% SSRI (escitalopram, sertraline) and SNRI in 68% (duloxetine, extended-release venlafaxine). The primary outcome measure was change from baseline MADRS total score at the end of week 4. Important secondary endpoints were the number of responders (MADRS score decrease of 50% or more), number of patients obtaining remission (MADRS score of equal to or less than 12) and change in CGI-S at week 4. Esketamine decreased MADRS scores more than placebo, -21.4 and -17.0 (MD -4.0; 95% CI, -7.3 to -0.64; P=0.020) at day 28, which was clinically and statistically significant.[7] Response and remission rates (based on MADRS) and CGI-S scores were not statistically different.

A randomized, withdrawal study was conducted to determine the efficacy of esketamine compared to placebo in a relapse prevention trial (SUSTAIN-1).[30] Patients were classified as direct-entry patients (which participated in screening, induction, optimization, maintenance and follow-up phases), and transfer-entry patients (responders from previous esketamine studies) who were in the optimization, maintenance and follow-up phases only. One-hundred seventy-six patients that were stable remitters during the maintenance phase were randomized to either 56-84 mg esketamine + oral antidepressant or to placebo + oral antidepressant for the primary analysis of relapse rates. A secondary endpoint was an analysis of relapse rates in patients who had a stable response in the optimization phase (n=121). Esketamine + oral antidepressant was associated with a relapse rate of 26.7% versus 45.3% in the placebo + antidepressant group (p=0.003/NNT 6).[30] For the secondary analysis of the number of patients with a stable response that experienced a relapse, 25.8% in the esketamine + antidepressant group and 57.6% in the placebo + antidepressant group had a relapse (p<0.001/NNT 3).[30] The mean exposure time was 17.7 weeks for both analyses.

TRANSFORM-1 was a randomized, double-blind, multi-center trial in 346 patients. Patients were randomized to fixed dose esketamine 56 or 84 mg or placebo with both groups also taking an oral antidepressant. After 4 weeks of treatment, mean change in MADRS scores were: -19.0 for esketamine 56 mg, -18.8 for esketamine 84 mg and -14.8 for the placebo group. Changes were not found to be statistically significant (p=0.088). A similarly designed trial (TRANSFORM-3) was done in elderly patients, 65 years and older (n=137). At four weeks, a mean change from placebo + antidepressant of -3.7 points on the MADRS scale was demonstrated, which was not statistically significant (p=0.059).

Limitations to the studies include small sample size and short treatment duration all efficacy studies. There is low external validity due to extensive exclusion criteria and the allowance of only four different oral antidepressants. The relapse prevention study biased trial results towards patients that were esketamine responders or remitters to treatment during the optimization phase. This study also increased the number of patients experiencing relapses after an interim analysis did not show superiority of esketamine + oral antidepressant compared to placebo + oral antidepressant. Patients were also started on a new oral antidepressant, in both groups, which could influence efficacy results in both groups.

Clinical Safety:
Common adverse events associated with esketamine are presented in **Table 7**.[9] Adverse events experienced in patients taking esketamine, with an incidence of at least 5% or more, and twice placebo rates in patients also taking antidepressants, where dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting and feeling drunk.[9] The most common psychological effects were dissociation, perceptual changes, derealization and depersonalization given esketamine. Precautions include cognitive impairment, embryo-fetal toxicity and increased blood pressure. See prescribing information for all warnings and precautions.

Table 7. Some of the Adverse Reactions Reported in Greater than or equal to 2% of Esketamine Treated Patients and More than Placebo[9]

Adverse Reaction	Esketamine + oral antidepressant (N=346)	Placebo + oral antidepressant (N=222)
Dissociation	41%	9%
Dizziness	29%	8%
Nausea	28%	9%
Sedation	23%	9%
Vertigo	23%	3%
Anxiety	13%	6%
Increased blood pressure	10%	3%
Vomiting	9%	2%
Feeling Drunk	5%	0.5%
Feeling abnormal	3%	0%

Esketamine REMS Program Requirements[9]

- Pharmacies must be certified in the REMS in order to dispense to certified healthcare setting.
- Healthcare setting must be certified in the REMS in order to treat patients with esketamine nasal spray.
- Patient must be enrolled in the esketamine REMs to receive treatment.
- Provider must supervise administration, post-administration monitoring and provide patient education about potential serious outcomes associated with sedation and dissociation.
- Patients must be observed as least 2 hours administration for resolution of dissociation effects and sedation.
- Blood pressure should also be monitored for transient blood pressure increases lasting around 4 hours. Baseline blood pressure prior to administration and blood pressure 40 minutes post-dose should be taken to monitor for transient blood pressure increases.

A 52-week safety study (SUSTAIN-2) was done in 802 patients with treatment resistant depression, mean age of 52 years, and 63% females.[8] Patients were entered into a 4-week induction phase followed by a 48 day optimization and maintenance phase. The primary outcome was to evaluate safety with the change in MADRS score being a secondary outcome. Approximately 9.5% of patients in the esketamine + antidepressant group discontinued due to adverse events by the end of the maintenance phase and 4.1% of patients in the placebo + antidepressant group. Concerning adverse events of acute hypertension, severe dissociation and severe sedation were seen in 2.3%, 1.4% and 0.5% of patients, respectively during the induction phase and 3.0%, 0.7% and 0.2% of patients, respectively during the optimization/maintenance phase.[8]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Remission of depressive symptoms
2) Relapse of depressive episode
3) Symptom reduction (as determined by a validated scale)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in MADRS score at day 28

Table 8. Pharmacology and Pharmacokinetic Properties of Esketamine.

Parameter	
Mechanism of Action	non-competitive N-methyl D-aspartate (NMDA) receptor antagonist with the exact antidepressant mechanism unknown
Nasal Bioavailability	48%
Distribution and Protein Binding	709 Liters; protein binding 43-45%
Elimination	<1% unchanged in the urine
Half-Life	7-12 hours
Metabolism	P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19

Table 9. Esketamine Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Popova, et al[7] Phase 3, DB, PC, RCT	1. Esketamine nasal spray (56 -84 mg) + oral antidepressant twice weekly† (E) 2. Placebo nasal spray + oral antidepressant twice weekly† (P) 28 days	Demographics: Age: 45 years Male: 38% SNRI at baseline: 68% Average MADRS score: 37 Key Inclusion Criteria: - 18-64 years - single episode (greater than or equal to 2 years) or recurrent major depressive disorder without psychotic features - score of 34 or greater on the IDS-C - diagnosis of treatment resistant depression* Key Exclusion Criteria: - current or recent homicidal suicidal ideation/intent or suicidal behavior within the past 6 months - psychotic disorder, MDD with psychotic features, bipolar or related disorders, antisocial, histrionic or narcissistic personality disorder, OCD or intellectual disability - seizures, uncontrolled hypertension - substance use disorder	mITT: 1. 116 2. 111 PP: 1. 98 2. 99 Attrition: 1. 16% 2. 11%	Change in baseline of MADRS score at day 28: E: -21.4 points P: -17.0 points E vs. P LSMD -4.0 (95% CI, -7.31 to -0.64) p-value: 0.020 Secondary Endpoints: MADRS clinical response: E: 9 (7.9%) P: 5 (4.6%) p-value: 0.321	 NA NS	Discontinuations due to Adverse Events: E: 8 (7.0%) P: 1 (0.9%) Dissociation: E: 30 (26%) P: 4 (3.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1, computer generated. Baseline characteristics similar except for a higher number of females in the esketamine group compared to placebo, 66% versus 58%. Performance Bias: (low) Double-blind design, investigators, patients, study team, site staff, principle investigator were all blinded to treatment allocation. Identical packaging was used to maintain blinding and well as flavoring agent. Detection Bias: (low) Data analysis was blinded and MADRS assessments were done by independent (remote) blinded evaluators. Attrition Bias: (high) attrition was high both groups. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer and response and remission analysis was post-hoc. **Applicability**: Patient: Applies to patients with severe depression taking oral antidepressants that do not have other personality disorders (low external validity) and have had an inadequate response to at least two antidepressants. Studies in patients 65 and older found no benefit compared to placebo. Intervention: Appropriate dose based on pharmacokinetic studies. Comparator: Placebo appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: MADRS is a validated tool to assess therapeutic efficacy of antidepressants. Setting: Thirty-nine centers (26% in US study sites).

1. Daly, et al[30] SUSTAIN-1 Phase 3, DB, PC, MC, RCT	1. Esketamine nasal spray (56 -84 mg) + oral antidepressant twice weekly (E) 2. Placebo nasal spray + oral antidepressant twice weekly† (P) Mean exposure: 17.7 weeks - 4-week screening and prospective observation phase (direct-entry patients only∝) - 4-week open-label induction phase (direct-entry patients only∝) - 12-week optimization phase (direct-entry or transfer-entry patients∝) - event driven maintenance phase - 2-week post-treatment follow-up	Demographics: Age: 46.3 years Female: 66.3% Average MADRS score: 38.5 Key Inclusion Criteria: - 18-64 years - Achieved clinical treatment response‡ to esketamine nasal spray in 1 of 2 previous trials - single episode (greater than or equal to 2 years) or recurrent major depressive disorder without psychotic features - score of 34 or greater on the IDS-C - diagnosis of treatment resistant depression* - MADRS score of 28 or higher Key Exclusion Criteria: - suicidal behavior within the past year - current or recent homicidal or suicidal ideation or intent - MDD with psychotic features, personality disorder, OCD or intellectual disability - seizures, uncontrolled hypertension - moderate to severe substance or alcohol use disorder within the last 6 months - history of ketamine use disorder	mITT (remission): 1. 90 2. 86 PP (remission): 1. 82 2. 77 Attrition (remission): 1. 9% 2. 10% mITT (stable response): 1. 62 2. 59 PP (stable response): 1. 57 2. 56 Attrition (stable response): 1. 8% 2. 5%	Relapse in Patient who were in Stable Remission: E: 24 (26.7%) P: 39 (45.3%) HR 0.49 (95%CI, 0.29 to 0.84) p-value: 0.003 Secondary Endpoints: Relapse in patients who had a Stable Response: E: 16 (25.8%) P: 34 (57.6%) HR 0.30 (95% CI, 0.16 to 0.55) p-value: <0.001	19/6 32/3	Dysgeusia: E: 41 (27%) P: 10 (6.9%) Dissociation: E: 35 (23%) P: 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized based on if obtained stable remission or response by a computer-generated schedule. Performance Bias: (unclear) Double-blind design but details not provided. Identical packaging was used to maintain blinding. Detection Bias: (low) Data analysis was blinded and MADRS assessments were done by independent (remote) blinded evaluators. Attrition Bias: (low) attrition was low both groups. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer. **Applicability**: Patient: Applies to patients with treatment resistant depression taking oral antidepressants that do not have other personality disorders (low external validity) and had a positive response to esketamine treatment. Intervention: Appropriate dose based on pharmacokinetic studies. Comparator: Placebo, with oral antidepressant, appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: Remission is an appropriate outcome. Setting: Centers in US, Europe and Canada.

Key: * Treatment-resistant depression: nonresponse to an adequate trial (dosage, duration, and adherence) of at least 2 antidepressants in the current episode (of which one was observed prospectively); † Newly initiated open-label oral antidepressant (escitalopram, sertraline, duloxetine or venlafaxine) administered daily, ‡ Clinical response was defined as a ≥50% reduction in MADRS score by day 2 maintained to the end of the double-blind treatment phase with one excursion (i.e., a ≥25% reduction relative to baseline MADRS was allowed on day 8, 15 or 22); ∝ Direct-entry patients were underwent the screening and inductions phase and all patients who had a clinical response‡ at the end of the induction phase went into the optimization, maintenance and follow-up phases

Abbreviations: ARR = absolute risk reduction; CGI = Clinical Global Impression-Improvement response; CI = confidence interval; IDS-C =Inventory of Depressive Symptomatology- Clinician Rating; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OCD = obsessive compulsive disorder; PC = placebo-controlled; PP = per protocol; PPD = post-partum depression; SNRI = serotonin norepinephrine reuptake inhibitor

NEW DRUG EVALUATION: Brexanolone (Zulresso)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Brexanolone is a GABA $_A$ receptor positive modulator (similar to progesterone, which is reduced after pregnancy) indicated for the treatment of moderate to severe PDD in adults.[11] Brexanolone is administered by IV and titrated from a starting dose of 30 mcg/kg/hour up to a maximum dose of 90 mcg/kg/hour and back down again, over 60 hours. FDA approval was based on 2, double-blind, randomized, identical phase 3 trials (n= 226). Women were eligible if they were 18-45 years and had a HAM-D score indicating severe to very severe depression. In the first study, the mean age was 27 years, 25% had current antidepressant use at baseline, and the average HAM-D score was 29.[11] In the second study, the mean age was 28 with antidepressant use in 18% at baseline and average HAM-D score of 23.[10] Patients were followed for a total of 30 days. The mean time of brexanolone administration was approximately 4 months after delivery. The primary endpoint was change in the 17-item HAM-D total score from baseline at 60 hours. An important secondary endpoint was CGI-I response at 60 hours, which was a change of 1-2 points on the CGI-I scale.

In the first study, patients were randomized 1:1:1 to brexanolone 60 mcg/kg/hr (BX60), brexanolone 90 mcg/kg/hour (BX90) or placebo infusion over 60 hours (**Table 12**).[10] The changes in HAM-D scores were statistically significant compared to placebo for the BX60 and BX90 dose, -5.5 and -3.7 points, respectively.[10] Changes in the CGI-I response compared to placebo were statistically significant with 26-31% of patients responding to treatment (NNT of 4 for both doses). In the second study, BX90 decreased HAM-D scores by -2.5 points (p=0.016) more than placebo, which is not considered a clinically meaningful change. The change in CGI-I response was greater than placebo by 39% (NNT of 3).[10]

Trial limitations include small sample sizes and short-term durations. Adverse events associated with brexanolone may have alerted investigators to treatment randomization, potentially causing investigator bias. Background antidepressants were allowed and used in approximately 30% of the study participants.

Clinical Safety:
Common adverse reactions which occurred at least 5% more often and at least twice the rate of placebo were sedation/somnolence, dry mouth, loss of consciousness and flushing/hot flush (**Table 10**).[11] Dose interruption or reduction due to sedation and somnolence occurred more frequently in patients receiving brexanolone compared to placebo, 5% versus 0%, respectively. Loss of consciousness also occurred in 4% of brexanolone treated patients compared to none in the placebo group. Sedative effects should be evaluated every 2 hours during the infusion. Consequently, there is a boxed warning, due to risk of excessive sedation or sudden loss of consciousness. For these reasons, while administering brexanolone patients should have continuous pulse oximetry monitoring and brexanolone is only available through a REMS program.

Requirement of the REMS program are:

- healthcare facilities must be enrolled in the program and brexanolone must only be administered to patients who are enrolled in the program,
- pharmacies must be certified with the program and must only dispense brexanolone to healthcare facilities who are certified in the brexanolone REMS,
- patients must be enrolled in the brexanolone REMS prior to administration, and
- wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies.[11]

Breast feeding was not permitted during the trials. It is estimated that 2% or less of the maternal dose would be excreted into breast milk.

Table 10. Adverse Reactions Reported in Greater than or equal to 2% of Brexanolone Treated Patients and More than Placebo[11]

Adverse Reaction	Placebo	Brexanolone 60 mcg/kg/hour	Brexanolone 90 mcg/kg/hour
Sedation, somnolence	6%	21%	13%
Dizziness, presyncope, vertigo	7%	13%	12%
Dry mouth	1%	11%	3%
Loss of consciousness	0	5%	3%
Flushing, hot flush	0	5%	2%
Diarrhea	1%	3%	2%
Oropharyngeal pain	0	3%	2%
Tachycardia	0	0	3%
Dyspepsia	0	0	2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of depressive symptoms
2) Relapse of depressive episode
3) Symptom reduction (as determined by a validated scale)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

2) Change in 17-item HAM-D total score at 60 hours

Table 11. Pharmacology and Pharmacokinetic Properties of Brexanolone

Parameter	
Mechanism of Action	Thought to be due to its positive allosteric modulation of $GABA_A$ receptors
Oral bioavailability	NA
Distribution and Protein Binding	3 Liters/kg >99%
Elimination	47% in the feces and 42% in the urine
Half-Life	9 hours
Metabolism	Non-CYP based pathways via three main routes (keto-reduction, glucuronidation, and sulfation.

Abbreviations: Not applicable

Table 12. Brexanolone Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Meltzer-Brody, et al[10] Phase 3, DB, PC, RCT	1. Brexanolone 90 mcg/kg per hour IV over 60 hours (BX90) 2. Brexanolone 60 mcg/kg per hour IV over 60 hours (BX60) 3. Placebo IV over 60 hours (P)	Demographics: Age: 27 years Depression: 43% Previous PPD: 36% Baseline antidepressant use: 25% Average HAM-D score: 29 Key Inclusion Criteria: - 18-45 years - 6 months or less post-partum at screening with PPD - qualifying 17-item HAM-D score (greater than or equal to 26) Key Exclusion Criteria: - renal failure requiring dialysis - anemia - allergy to allopregnanolone or progesterone - history of schizophrenia, bipolar disorder, schizoaffective disorder	mITT: 1. 41 2. 38 3. 43 PP: 1. 36 2. 35 3. 42 Attrition: 1. 9% 2. 19% 3. 7%	Change in 17-item HAM-D total score at 60 hours: BX90: -17.7 points BX 60: -19.5 points P: -14.0 points BX90 vs. P LSMD -3.7 (95% CI, -6.9 to -0.5) p-value: 0.0252 BX 60 vs. P LSMD -5.5 (95% CI, -8.8 to -2.2) p-value: 0.0013 Secondary Endpoints: CGI-I response: BX90: 32 (82%) BX60: 31 (87%) P: 24 (56%) BX90 vs. P: OR 4.0 (95% CI, 1.4 to 11.6) p-value: 0.0095 BX60 vs. P: OR 4.0 (95% CI, 1.3 to 11.7) p-value: 0.0131	NA 26/4 31/4	Discontinuations due to Adverse Events: BX90: 0 BX60: 1 (3%) P: 1 (2%) Severe Adverse Event: BX90: 0 BX60: 1 (3%) P: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1:1, 25% manually and 75% electronically. Baseline characteristics were well matched except for there was a lower number of patients with an anxiety diagnosis in the placebo group compared to brexanolone groups, 33%, 43%, and 47%, respectively. Performance Bias: (unclear) Double-blind design, investigators, patients, study team, site staff, principle investigator were all blinded to treatment allocation. Infusion rates were matched to avoid unblinding. Detection Bias: (unclear) Scores were determined by masked site investigators and approximately 50% were recorded. However, adverse events associated with brexanolone could potentially alert providers to randomization. Scoring may be subject to investigator bias. Attrition Bias: (high) attrition was high in the 60 mcg brexanolone group, with differences greater than 10% versus comparators. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer **Applicability**: Patient: Applies to women with severe depression, with or without current antidepressant use. Intervention: Appropriate dose based on pharmacokinetic studies Comparator: Placebo appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: HAM-D is a validated tool to assess therapeutic efficacy of antidepressants. Setting: Thirty centers in the USA.
2. Meltzer-Brody, et al[10] Phase 3, DB, PC, RCT	1. Brexanolone 90 mcg/kg per hour IV over 60 hours (BX90) 3. Placebo IV over 60 hours (P)	Demographics: Age: 28 years Depression: 29% Previous PPD: 37% Baseline antidepressant use: 18% Average HAM-D score: 23 Key Inclusion Criteria:	mITT: 1. 51 2. 53 PP: 1. 48 2. 52 Attrition: 1. 6%	Change in 17-item HAM-D total score at 60 hours: BX90: -14.6 P: -12.1 LSMD -2.5 (95% CI, -4.5 to -0.5) p-value: 0.0160 Secondary Endpoints: CGI-I response:	NA	Discontinuations due to Adverse Events: BX90: 2 (4%) P: 0 Severe Adverse Event: BX90: 2 (4%) P: 1 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1, baseline characteristics similar except for a higher number of patients in the placebo group with a history of depression compared to the treatment group, 33% and 24%, respectively. Performance Bias: See above Detection Bias: See above Attrition Bias: (low) low attrition in each group. Results analyzed with a mITT analysis.

		- 18-45 years - 6 months or less post-partum at screening with PPD - qualifying 17-item HAM-D score (20-25) Key Exclusion Criteria: - see above	2. 2%	BX90: 39 (80%) P: 29 (56%) BX90 vs. P: OR 5.0 (95% CI, 2.0 to 12.5) p-value: 0.0005	39/3			Reporting Bias: See above **Applicability**: Patient: Applies to women with moderate to severe depression, with or without current antidepressant use. Intervention: See above Comparator: See above Outcomes: See above Setting: See above
Abbreviations: ARR = absolute risk reduction; CGI =Clinical Global Impression-Improvement response; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; LSMD= least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PP = per protocol; PPD = post-partum depression								

References:

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL status
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	NORPRAMIN	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluoxetine HCl	SARAFEM	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
imipramine HCl	TOFRANIL	TABLET	Y
maprotiline HCl	MAPROTILINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y

protriptyline HCl	PROTRIPTYLINE HCL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
trimipramine maleate	SURMONTIL	CAPSULE	Y
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24	V
desvenlafaxine	KHEDEZLA	TAB ER 24	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
desvenlafaxine fumarate	DESVENLAFAXINE FUMARATE ER	TAB ER 24	V
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	V
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	V
duloxetine HCl	CYMBALTA	CAPSULE DR	V
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
nefazodone HCl	NEFAZODONE HCL	TABLET	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V

paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
selegiline	EMSAM	PATCH TD24	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
amoxapine	AMOXAPINE	TABLET	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, and Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well- treated major depressive disorder experiencing SSRI-induced sexual dysfunction.

Introduction: Sexual dysfunction is common with serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), and does not resolve in most patients. Vortioxetine, an antidepressant with a multimodal mechanism of action, has shown low rates of sexual dysfunction in previous major depressive disorder (MDD) trials.

Aim: This study compared the effects of vortioxetine and escitalopram on sexual functioning in adults with well-treated MDD experiencing treatment-emergent sexual dysfunction (TESD).

Methods: Participants treated with, and responding to, citalopram, paroxetine, or sertraline were randomized to switch to either vortioxetine (10/20 mg; n = 225) or escitalopram (10/20 mg; n = 222) for 8 weeks. Sexual function was assessed using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), and antidepressant efficacy was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions (CGI) scale, and Profile of Mood States brief form (POMS-brief). Safety and tolerability were also assessed.

Main Outcome Measures: The primary endpoint was change from baseline in the CSFQ-14 total score after 8 weeks of treatment. The MADRS, CGI, and POMS-brief were used to assess antidepressant efficacy. Safety was assessed via adverse events, vital signs, electrocardiograms, laboratory values, weight, and physical examination findings.

Results: Vortioxetine showed significantly greater improvements in CSFQ-14 total score (8.8 ± 0.64, mean ± standard error) vs. escitalopram (6.6 ± 0.64; $P = 0.013$). Benefits vs. escitalopram were significant on four of five dimensions and all three phases of sexual functioning assessed by the CSFQ-14 ($P < 0.05$). Antidepressant efficacy continued in both groups, with similar, but slight, improvements in MADRS and CGI scores. Vortioxetine and escitalopram had similar clinical efficacy profiles in this study, with safety profiles similar to previous trials. Nausea (n = 9, 4.0%) was the most common treatment-emergent adverse event leading to discontinuation of vortioxetine.

Conclusion: Switching antidepressant therapy to vortioxetine may be beneficial for patients experiencing sexual dysfunction during antidepressant therapy with SSRIs.

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to April Week 1 2019
Search Strategy:

#	Searches	Results
1	amitriptyline.mp. or Amitriptyline/	8629
2	bupropion.mp. or Bupropion/	4249
3	citalopram.mp. or Citalopram/	6187
4	desipramine.mp. or Desipramine/	7653
5	doxepine.mp.	86
6	escitalopram.mp. or Citalopram/	5085
7	fluoxetine.mp. or Fluoxetine/	12328
8	fluvoxamine.mp. or Fluvoxamine/	2686
9	imipramine.mp. or Imipramine/	12752
10	maprotiline.mp. or Maprotiline/	1259
11	mirtazapine.mp. or Mirtazapine/	1873
12	nortriptyline.mp. or Nortriptyline/	2930
13	paroxetine.mp. or Paroxetine/	5672
14	protriptyline.mp. or Protriptyline/	399
15	sertraline.mp. or Sertraline/	4304
16	trimipramine.mp. or Trimipramine/	494
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
18	clomipramine.mp. or Clomipramine/	3766
19	desvenlafaxine.mp. or Desvenlafaxine Succinate/	348
20	duloxetine.mp. or Duloxetine Hydrochloride/	2051
21	isocarboxazid.mp. or Isocarboxazid/	404
22	levomilnacipran.mp.	54
23	nefazodone.mp.	727
24	phenelzine.mp. or Phenelzine/	1595
25	selegiline.mp. or Selegiline/	2723
26	tranylcypromine.mp. or Tranylcypromine/	2172

27	venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
28	vilazodone.mp. or Vilazodone Hydrochloride/	148
29	vortioxetine.mp. or Vortioxetine/	249
30	amoxapine.mp. or Amoxapine/	436
31	trazodone.mp. or Trazodone/	1845
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	66706
33	limit 32 to (english language and humans)	39890
34	limit 33 to yr="2017 -Current"	1640
35	limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	155

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO™ safely and effectively. See full prescribing information for SPRAVATO™.

SPRAVATO™ (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)**
- **Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)**
- **SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)**

----------INDICATIONS AND USAGE----------

SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. (1)

Limitations of Use: SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)
- Assess blood pressure prior to and after administration. (2.1)
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment. (2.2)
- See Full Prescribing Information for recommended dosage during the induction and maintenance phases. (2.2)
- See Full Prescribing Information for important administration instructions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

----------CONTRAINDICATIONS----------

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Increases in Blood Pressure:* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment:* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity:* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZULRESSO safely and effectively. See full prescribing information for ZULRESSO.

ZULRESSO™ (brexanolone) injection, for intravenous use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

See full prescribing information for complete boxed warning.

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO. (5.1)**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). (5.1)**
- **ZULRESSO is available only through a restricted program called the ZULRESSO REMS. (5.1, 5.2)**

INDICATIONS AND USAGE

ZULRESSO is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

- A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion (2.1).
- Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows (2.2):
  - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
  - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
  - 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
  - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
  - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour
- Dilution required prior to administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors: Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Avoid use in patients with end stage renal disease (ESRD). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with major depressive disorder, anxiety disorder or post-traumatic stress disorder
Intervention	Antidepressant
Comparator	Placebo or active treatment comparison
Outcomes	Symptom improvement, response or remission of depression
Timing	At onset of symptoms
Setting	Outpatient and inpatient (brexanolone)

Appendix 6: Proposed Safety Edits

Brexanolone (Zulresso)

Goal(s):

- To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:

One time use only.

Requires PA:

- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
4. Is the patient an adult with moderate to severe post-partum depression?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 7/19 (KS)
Implementation: TBD

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for maintenance dosing of esketamine (for determining response to therapy)?	**Yes:** Go to #9	**No:** Go to #5
5. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Does the patient have treatment resistant depression (failure of two antidepressants which were given for at least 6-8 weeks at FDA approved doses)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
7. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
8. Does the patient have documentation of any of the following: • Aneurysmal vascular disease or arterial venous malformation OR • Intracerebral hemorrhage OR • Pregnancy OR • Uncontrolled hypertension	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

Approval Criteria		
9. Is there documentation that the patient demonstrated an adequate response during the induction phase (an improvement in depressive symptoms)?	**Yes:** Approve for up to 6 months (maximum of 12 per month)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 7/19 (KS)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Hepatitis C, Direct-Acting Antivirals

Date of Review: September 2019

Date of Last Review: September 2018
Literature Search: 08/2018 – 08/2019

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There is insufficient evidence to evaluate the use of direct acting antivirals (DAAs) in the treatment of acute HCV infection.[1]
- There is no new comparative data demonstrating superior efficacy or safety of one DAA over another in the treatment of chronic hepatitis C (CHC) in decreasing mortality, hepatocellular carcinoma (HCC) or complications of liver disease.
- There is low to insufficient evidence that glecaprevir and pibrentasvir (G/P) is safe and effective in pediatric patients ages 12 to 17 with CHC without cirrhosis in achieving sustained virologic response (SVR).

Recommendations:
- Approve updated prior authorization (PA) criteria (**Appendix 5**).
- Review comparative costs in executive session.

Summary of Prior Reviews and Current Policy
- There is low quality evidence that all of the DAA regimens are effective in achieving a SVR rate of greater than or equal to 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks sofosbuvir/velpatasvir (SOF/VEL) may be modestly superior to 12 weeks SOF + ribavirin (RBV) in patients with genotype (GT) 2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT 3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.

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- Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
- There is no direct, randomized prospective evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.

- The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease.
- Current drug policies in place approve treatment for all patients with CHC, regardless of fibrosis severity or history of substance use disorder.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing any medication in **Table 1** on clinically relevant outcomes to active controls, or placebo if needed, was conducted. Non-randomized data will be considered if clinically important outcomes including mortality and HCC are included. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza™ and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8 - 24 weeks
Mavyret™	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks

		inhibitor or an NS3/4a protease inhibitor			
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 TE with NS5A inhibitor; GT 1a or 3 TE with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks
Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin; TE: treatment-experienced					

New Systematic Reviews:
After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

A Cochrane Collaboration systematic review was published in December 2018 to assess the comparative benefits and harms of pharmacologic interventions in the treatment of acute HCV, as it remains controversial if any intervention is beneficial in acute HCV infection.[1] Randomized trials evaluating interferons as well as DAAs were included. Overall, 13 trials met inclusion criteria (n=488). However, none of the trials compared DAAs versus other interventions. At this time, there is insufficient evidence to evaluate the use of DAAs in the treatment of acute HCV infection.

New Guidelines:
None Identified

New Formulations:
None Identified

New FDA Safety Alerts:
None Identified

New Indications:
In April 2019, the FDA approved Mavyret™ (glecaprevir and pibrentasvir [G/P]) to treat all six genotypes in pediatric patients ages 12 to 17 who weigh at least 45 kg without cirrhosis or with compensated cirrhosis.[2] Approval was based on one, unpublished, open-label study designed to assess the pharmacokinetics, safety and efficacy of G/P 300 mg/120 mg once daily for 8, 12 or 16 weeks in patients ages 12 to 17 with CHC without cirrhosis. The primary outcome was area under the curve and SVR12 was a secondary endpoint. The majority of patients (79%) had HCV GT 1, and 77% were treatment-naïve.[2] The overall SVR12 rate was 100% (47/47).[2] This data remains unpublished and cannot be fully assessed for risk of bias. Approval in patients with compensated cirrhosis and GTs 5 or 6 was based on comparable exposure of G/P between adolescents and adults.

References:

1. Kalafateli M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Pharmacological interventions for acute hepatitis C infection. *The Cochrane database of systematic reviews.* 2018;12:Cd011644.
2. Mavyret (glecaprevir and pibrentasvir) Prescribing Information. Abbvie Pharmaceuticals. 4/2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209394s006lbl.pdf.
3. Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of Glecaprevir and Pibrentasvir in Patients with Genotype 1 Hepatitis C Virus Infection with Treatment Failure after NS5A Inhibitor Plus Sofosbuvir Therapy. *Gastroenterology.* 2019.
4. Esteban R, Pineda JA, Calleja JL, et al. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis. *Gastroenterology.* 2018;155(4):1120-1127.e1124.
5. Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. *The lancet Gastroenterology & hepatology.* 2019;4(1):45-51.
6. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet (London, England).* 2019;393(10179):1453-1464.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
elbasvir/grazoprevir	ZEPATIER	TABLET	Y
glecaprevir/pibrentasvir	MAVYRET	TABLET	Y
sofosbuvir/velpatas/voxilaprev	VOSEVI	TABLET	Y
sofosbuvir/velpatasvir	EPCLUSA	TABLET	Y
sofosbuvir/velpatasvir	SOFOSBUVIR-VELPATASVIR	TABLET	Y
daclatasvir dihydrochloride	DAKLINZA	TABLET	N
ledipasvir/sofosbuvir	HARVONI	TABLET	N
ledipasvir/sofosbuvir	LEDIPASVIR-SOFOSBUVIR	TABLET	N
ombita/paritap/riton/dasabuvir	VIEKIRA PAK	TAB DS PK	N
sofosbuvir	SOVALDI	TABLET	N

Appendix 2: New Clinical Trials

A total of 99 citations were manually reviewed from the initial literature search. After further review, 96 citations were excluded because of wrong study design, comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Lok, et al.[3] Open-label RCT, phase 3b	No Cirrhosis 1. G/P x 12 weeks 2. G/P x 16 weeks Compensated Cirrhosis: 3. G/P + RBV x 12 weeks 4. G/P + RBV x 16 weeks	HCV GT 1 with previous treatment failure from sofosbuvir + NS5A inhibitor (n=177)	SVR12	SVR12: 1. 70/78 (90%) 2. 46/49 (94%) 3. 18/21 (86%) 4. 28/29 (97%)
Esteban, et al. [4] Open-label RCT, phase 2	SOF/VEL vs. SOF/VEL + RBV X 12 weeks	Adults with HCV GT 3 and compensated cirrhosis (n=201)	SVR12	SVR12: SOF/VEL: 92/101 (95%; 95% CI 84 to 96) SOF/VEL + RBV: 99/103 (96%; 95% CI 90.4 to 98)

Abbreviations: G/P: glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis V virus; NS5A = nonstructural protein 5A; RBV = ribavirin; RCT = randomized clinical trial; SOF/VEL = sofosbuvir and velpatasvir; SVR12 = sustained virologic response 12 weeks after treatment

Table 2. Description of Prospective Observational Trials on Clinical Outcomes

Study	Comparison	Population	Primary Outcome	Results	
Carrat et al.[6] Prospective, cohort study	DAA vs. no DAA	Patients with CHC without HIV, HBV, and decompensated cirrhosis (n=9895)	All-cause mortality, hepatocellular carcinoma (HCC), or liver transplantation	All-cause mortality (n per person years) DAA: 129/13,626 No DAA: 89/12,709 HR* 0.48; 95% CI 0.33-0.70 Decompensated Cirrhosis: DAA: 74/13520 No DAA: 32/12,698 HR* 1.14; 95% CI 0.57 to 2.27	HCC: DAA: 187/13,375 No DAA: 71/12,660 HR* 0.66; 95% CI 0.46 to 0.93

Abbreviations: CHC = chronic liver disease; CI = confidence interval; DAA = direct acting antiviral; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HR = hazard ratio; n = number

*Multivariable adjusted HR

Appendix 3: Abstracts of Comparative Clinical Trials

1.Efficacy of Glecaprevir and Pibrentasvir in Patients with Genotype 1 Hepatitis C Virus Infectionwith Treatment Failure after NS5A Inhibitor Plus Sofosbuvir Th erapy Gastroenterology. 2019 Aug 8. pii: S0016-5085(19)41199-2. doi: 10.1053/j.gastro.2019.08.008. [Epub ahead of print]

BACKGROUND/AIMS:
Treatment options are limited for patients with hepatitis C (HCV) infection with treatment failure after sofosbuvir plusan NS5A inhibitor. There are some data for the efficacy of glecaprevir/pibrentasvir (G/P) in these patients. We performed a randomized trial of the safety and efficacy of 12 and 16 weeks of G/P, with or without ribavirin, in patients with HCV genotype 1 infection with treatment failureafter sofosbuvir and an NS5A inhibitor.

METHODS:
We performed a phase 3b, open label study of patients with chronic HCV genotype 1 infection who received
previous treatmentwith sofosbuvir plus an NS5A inhibitor. Patients without cirrhosis were randomly assigned to groups that received G/P for 12 weeks (n=78, group A) or 16 weeks (n=49, group B). Patients with compensated cirrhosis were randomly assigned to groups that received G/P and ribavirin for 12 weeks (n=21, group C) or G/P for 16 weeks (n=29, group D). The primary endpoint was a sustained virologic response 12 weeks aftertreatment (SVR12). Samples collected at baseline and at time of treatment failure were sequenced for resistance-associated substitutions (RASs) in NS3 and NS5A.

RESULTS:
Of the 177 patients in the 4 groups, 81% were men, 79% had HCV genotype 1a infection, and 44% were black. Proportions of patients with an SVR12 in groups A, B, C, and D were 90%, 94%, 86%, and 97%, respectively. The treatment failed in 13 patients with HCV genotype 1a infection (7.3%), 6 in group A (7.9%), 3 in group B (6.1%), 3 in group C (14.3%), and 1 in group D (3.4%). Most patients had baseline RASs in NS5A. Treatment-emergent RASs in NS3 and NS5A were observed in 9 and 10 patients with treatment failure, respectively. G/P was well tolerated. Ribavirin increased adverse events but did not increase efficacy.

CONCLUSIONS:
In a randomized study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvirplus an NS5A inhibitor, 16 weeks treatment with G/P produced an SVR12 in more than 90% of patients, including those with compensated cirrhosis.

2. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis.

Gastroenterology. 2018 Oct;155(4):1120-1127.e4. doi: 10.1053/j.gastro.2018.06.042. Epub 2018 Jun 27.

BACKGROUND & AIMS:
In phase 3 trials and real-world settings, smaller proportions of patients with genotype 3 hepatitis C virus (HCV) infection and cirrhosis have a sustained virologic response 12 weeks after treatment (SVR12) with the combination of sofosbuvir and velpatasvir than in patients without cirrhosis. It is unclear whether adding ribavirin to this treatment regimen increases SVRs in patients with genotype 3 HCV infection and cirrhosis.

METHODS:

We performed a phase 2 trial of 204 patients with genotype 3 HCV infection and compensated cirrhosis (mean age 51 ± 7.4 years) at 29 sites in Spain from August 19, 2016 through April 18, 2017. Patients were assigned to groups given sofosbuvir and velpatasvirfor 12 weeks (n = 101) or sofosbuvir and velpatasvir plus ribavirin for 12 weeks (n = 103). The primary efficacy end point was SVR12.

RESULTS:
The overall rates of SVR12 were 91% (92 of 101; 95% CI 84-96) for the sofosbuvir-velpatasvir group and 96% (99 of 103; 95% CI 90-99) for the sofosbuvir-velpatasvir plus ribavirin group. In the sofosbuvir-velpatasvir group, a smaller proportion of patients with baseline resistance-associated substitutions (RASs) in nonstructural protein 5A (NS5A) achieved an SVR12 (84%) than did patients without (96%). In the sofosbuvir-velpatasvir plus ribavirin group, baseline RASs had less effect on the proportion of patients with an SVR12 (96% for patientswith baseline RASs; 99% for patients without). The most common adverse events (which occurred in ≥10% of patients) were asthenia (12%) in the sofosbuvir-velpatasvir group and asthenia (27%), headache (24%), and insomnia (12%) in the sofosbuvir-velpatasvir plus ribaviringroup.

CONCLUSIONS:
Consistent with findings from previous studies, a high rate of patients (91% and 96%) with genotype 3 HCV infection and compensated cirrhosis achieved an SVR12 with sofosbuvir and velpatasvir, with or without ribavirin. Of patients treated with sofosbuvir and velpatasvir without ribavirin, fewer patients with baseline NS5A RASs achieved an SVR12 compared with patients without baseline NS5A.

3. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019 Apr 6;393(10179):1453-1464. doi: 10.1016/S0140-6736(18)32111-1. Epub 2019 Feb 11.

BACKGROUND:
Although direct-acting antivirals have been used extensively to treat patients with chronic hepatitis C virus (HCV) infection, their clinical effectiveness has not been well reported. We compared the incidence of death, hepatocellular carcinoma, and decompensated cirrhosis between patients treated with direct-acting antivirals and those untreated, in the French ANRS CO22 Hepather cohort.

METHODS:
We did a prospective study in adult patients with chronic HCV infection enrolled from 32 expert hepatology centres in France. We excluded patients with chronic hepatitis B, those with a history of decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation, and patients who were treated with interferon-ribavirin with or without first-generation protease inhibitors. Co-primary study outcomes were incidence of all-cause mortality, hepatocellular carcinoma, and decompensated cirrhosis. The association between direct-acting antivirals and these outcomes was quantified using time-dependent Cox proportional hazards models. This study is registered with ClinicalTrials.gov, number NCT01953458.

FINDINGS:
Between Aug 6, 2012, and Dec 31, 2015, 10 166 patients were eligible for the study. 9895 (97%) patients had available follow-up information and were included in analyses. Median follow-up was 33·4 months (IQR 24·0-40·7). Treatment with direct-acting antivirals was initiated during follow-up in 7344 patients, and 2551 patients remained untreated at the final follow-up visit. During follow-up, 218 patients died (129 treated, 89 untreated), 258 reported hepatocellular carcinoma (187 treated, 71 untreated), and 106 had decompensated cirrhosis (74 treated, 32 untreated). Exposure to direct-acting antivirals was associated with increased risk for hepatocellular carcinoma (unadjusted hazard ratio [HR] 2·77, 95% CI 2·07-3·71) and decompensated cirrhosis (3·83, 2·29-6·42). After adjustment for variables (age, sex, body-mass index, geographical origin, infection route, fibrosis score, HCV treatment-naive, HCV genotype, alcohol consumption, diabetes,

arterial hypertension, biological variables, and model for end-stage liver disease score in patients with cirrhosis), exposure to direct-acting antivirals was associated with a decrease in all-cause mortality (adjusted HR 0·48, 95% CI 0·33-0·70) and hepatocellular carcinoma (0·66, 0·46-0·93), and was not associated with decompensated cirrhosis (1·14, 0·57-2·27).

INTERPRETATION:
Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma and should be considered in all patients with chronic HCV infection.

Appendix 4: Medline Search Strategy

▼ **Search History** (32)

# ▲	Searches	Results
1	glecaprevir.mp.	62
2	pibrentasvir.mp.	70
3	mavyret.mp.	3
4	sofosbuvir.mp. or SOFOSBUVIR/	1776
5	velpatasvir.mp.	144
6	voxilaprevir.mp.	40
7	vosevi.mp.	4
8	epclusa.mp.	10
9	daclatasvir.mp.	682
10	daklinza.mp.	10
11	technivie.mp.	3
12	ombitasvir.mp.	340
13	paritaprevir.mp.	329
14	ritonavir.mp. or RITONAVIR/	6059

☐	15	dasabuvir.mp.	295
☐	16	simeprevir.mp. or SIMEPREVIR/	610
☐	17	ledipasvir.mp.	683
☐	18	harvoni.mp.	42
☐	19	antiviral agents.mp. or Antiviral Agents/	77301
☐	20	direct acting antivirals.mp.	1640
☐	21	protease inhibitors.mp. or Protease Inhibitors/	41739
☐	22	ribavirin.mp. or RIBAVIRIN/	14744
☐	23	ns5a inhibitors.mp.	203
☐	24	ns5b inhibitor.mp.	85
☐	25	Hepatitis C, Chronic/ or Hepatitis C/	61515
☐	26	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	94545
☐	27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	122268
☐	28	25 or 26	149285
☐	29	27 and 28	21142
☐	30	limit 29 to (english language and humans and yr="2018 -Current" and (clinical trial, phase iii or clinical trial, phase iv or meta analysis or randomized controlled trial or "systematic review"))	99
☐	31	from 30 keep 5, 7-8, 12, 19-21, 24-26, 42-43...	22
☐	32	from 31 keep 5-10, 12-13, 17-20	12

Hepatitis C Direct-Acting

Goals:

Approve use of cost-effective treatments supported by the medical evidence.
Provide consistent patient evaluations across all hepatitis C treatments.
Ensure appropriate patient regimen based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-16 weeks

Requires PA:

All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection (B18.2)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Has all of the following pre-treatment testing been documented: a. Genotype testing in past 3 years is required if the patient has cirrhosis, any prior treatment experience, and if prescribed a regimen which is not pan-genotypic; ~~b. Baseline HCV RNA level in past 6 months;~~ ~~c.~~b. Current HBV status of patient ~~d.~~c. Pregnancy test in past 30 days for a woman of child-bearing age; and ~~e.~~d. History of previous HCV treatment and outcome ~~f.~~e. Presence or absence of cirrhosis as clinically determined (e.g., clinical, laboratory, or radiologic evidence)? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status. HIV testing is also recommended, and modification of HIV or HCV treatment regimens may be necessary if there are significant drug-drug interactions.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment. Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
6. Does the patient have ~~clinical, radiologic or laboratory evidence of~~ complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?	**Yes:** Go to #7 .	**No:** Go to #8

Approval Criteria		
7. Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend prescriber document referral to a specialist prior to initiating treatment.
8. Is there attestation that the patient and provider will comply with case management to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load? Case management includes assessment of treatment barriers and offer of patient support to mitigate potential barriers to regimen adherence as well as facilitation of SVR12 evaluation to assess treatment success.	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #10	**No:** Go to #11
10. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #11 Document test and result.
11. Does the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #13
13. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or loss of follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #14
14. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *1/19; 11/18; 9/18 (MH); 1/18; 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *3/1/2019; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15*

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Drug Class Literature Scan: Tobacco Smoking Cessation

Date of Review: September 2019

Date of Last Review: July 2016
Literature Search: June 2016 – June 2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose of Review:
The purpose of this literature scan is to provide new comparative effectiveness and safety evidence for therapeutic agents indicated for smoking cessation.

Conclusions:
- Seven systematic reviews, 9 randomized controlled trials, and 1 clinical practice guideline were identified which evaluated smoking cessation interventions in patients with tobacco dependence.
- The identified literature supports current policy and prior authorization (PA) criteria for smoking cessation as there is no new current comparative evidence to demonstrate a difference in clinical efficacy or safety among FDA-approved pharmacological agents.
- No comparative evidence was found to favor the use of one specific smoking cessation intervention including pharmacotherapy (NRT gum, lozenge, inhaler, and/or transdermal patch, varenicline or bupropion), behavioral counseling, or combination therapy in any subpopulation.
- Warnings about safety were added to the Chantix® (varenicline) label. Chantix® is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated.

Recommendations:
- Recommend no changes to the current PDL based on new comparative evidence.
- Implement an age limit for varenicline and update PA criteria.
- Evaluate comparative costs in the executive session.

Summary of Prior Reviews and Current Policy
- High quality evidence identified from previous reviews demonstrated that combined pharmacotherapy and behavioral treatment were more effective than usual care, brief advice, or less intensive support in the treatment of tobacco dependence. In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all FDA-approved smoking cessation agents are covered including varenicline, bupropion and all forms of nicotine replacement therapy. Except for bupropion HCl, all covered products have associated quantity limits for utilization control. Use of varenicline beyond 12 weeks or preferred nicotine replacement therapy use beyond 6 months require prior authorization (PA) as do all of the nicotine cartridge and spray formulations. The PA criteria for these agents are listed in **Appendix 6**. The majority of utilization for smoking cessation agents include nicotine patch, varenicline, nicotine gum, and nicotine lozenges. Each quarter,

there are approximately 800 paid claims for smoking cessation agents. The representative smoking cessation agents included on the Oregon PDL are presented in **Appendix 1**.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. The population, interventions, comparators, outcomes, timing, and setting for the included studies are listed in **Appendix 5**.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A 2016 Cochrane systematic review evaluated the efficacy of behavioral and/or pharmacological treatments for tobacco cessation in those with chronic obstructive pulmonary disease (COPD).[1] The primary outcome was percentage of participants with continuous or prolonged abstinence over a period of six months or longer. Sixteen randomized controlled trials (RCTs) were included in the review (N=13,123), 4 of which were used for meta-analysis.[1] Two studies (n=625) showed that nicotine sublingual tablet and varenicline were effective for increased quit rates versus placebo (14% vs 5%, respectively; RD 0.09 (95% CI 0.03 to 0.15) and 18.4% vs 5.5% RD of 0.13 (95% CI 0.07 to 0.18)).[1] Two studies (n=915) demonstrated that bupropion had a positive impact on tobacco quit rates versus placebo (pooled RD 0.09 (95% CI 0.03 to 0.15)). Pooled results from all four studies with low heterogeneity reported high-quality evidence of benefit with combined high-intensity behavioral support and medication intervention compared to behavioral support and placebo (RD 0.10 (95% CI 0.07 to 0.14; I^2=0%).[1] Nortriptyline did not demonstrate statistical significance in quit rate versus placebo. The authors were unable to effectively pool data for comparisons between different pharmacological treatments due to trial variability and overall high and unclear risk of bias.[1]

A Cochrane systematic review assessed the effects of different types of tobacco cessation interventions in adults treated for substance use disorders.[2] Interventions included pharmacotherapy (NRT gum, lozenge, inhaler, and/or transdermal patch, or non-NRT drugs such as varenicline or bupropion), behavioral counseling, or combination therapy.[2] Thirty-five RCTs (N=5796) of participants aged 15 or older with active treatment for, or recovery from, alcohol or drug dependence were included. Primary outcome was point prevalence abstinence biochemically verified.[2] Low quality evidence from 11 studies (N= 1808) suggested for people in treatment or recovery from alcohol or other drug dependency, tobacco abstinence at 8 weeks to 6 months improved with pharmacotherapy compared to placebo or usual care (RR 1.88 95% CI 1.37 to 2.57). Similarly, low quality evidence from 12 RCTs (N=2229) suggested that for people in alcohol or drug treatment/recovery, tobacco abstinence at 13 weeks to 18 months was more successful with combined pharmacotherapy and counseling versus usual care or placebo RR 1.74 (95% CI 1.39 to 2.18).[2] The studies did not address differences between the individual pharmacological agents and data on adverse effects were limited.[2]

Another Cochrane review evaluated the effectiveness of various pharmacologic and behavioral strategies to assist smoking cessation in individuals younger than 20 years of age.[3] The primary outcome of interest was individual-level smoking cessation at six-month follow-up or longer.[3] Forty-one RCTs (N>13,000) were selected for review of which 4 identified pharmacologic interventions with either nicotine patches, nicotine gum, or bupropion.[3] The majority of the studies were judged to have unclear or high risk of bias in at least one domain.[3] Pooled results of nicotine replacement therapy studies failed to demonstrate significant differences in smoking cessation outcomes compared to placebo.[3] The analysis failed to find a statistically significant benefit of standard dose bupropion versus placebo either alone or in combination with NRT. [3]

A systematic review evaluated the effectiveness of smoking cessation interventions in patients with substance use disorders.[4] The primary outcome measure was self-reported continuous abstinence rates at 6 and 12 months verified biochemically. [4] The review included seventeen RCTs (N=2966) which focused on smoking cessation interventions in adult patients who recently completed or were in active treatment for substance use disorder with at least a 6-months follow-up. [4] Trial quality varied as many of the required details used in evaluation were not reported. [4] Interventions included counseling, NRT, cognitive behavioral treatment (CBT), motivational interviewing, bupropion or varenicline either alone or in combination.[4] For smokers with a history of alcohol dependence, one small study of found 21-mg nicotine patches significantly increased continuous abstinence at 6 months follow-up compared to a placebo patch (24% vs 6% respectively; NNT=6, p<.05). [4] A combination of behavioral support and medication was found to be beneficial in two studies that included substance use dependent patients. For outpatient alcohol-dependent smokers, one study of intensive therapy with 16 CBT sessions plus 16 weeks of nicotine patches plus 26 weeks of nicotine lozenges demonstrated at 6-months post-treatment, there was a statistically significant difference in point prevalence abstinence compared to a smoking cessation clinic referral (ARD 15%, p=0.03) but there was no significant difference observed at 12 months. [4] In stimulant dependent smokers, treatment for substance use plus weekly individualized counseling and bupropion resulted in a significantly higher point prevalence abstinence at 6 months compared to substance use treatment alone (25.5% vs 2.2% respectively; P < .001). [4] Eight of the studies failed to report a difference between smoking cessation interventions in substance use dependent patients at the 6 or 12-month follow-up time period. [4]

A systematic review and meta-analysis evaluated the cardiovascular safety of varenicline in adult tobacco users.[5] Thirty-eight RCTs (N=12,706) of mostly 12-weeks in duration compared varenicline 1 mg twice daily to placebo. [5] Primary clinical outcomes included cardiovascular serious adverse events (SAEs) and/or all-cause mortality within treatment period or within 30 days of discontinuation. [5] Four of the studies examined CVD patients, 17 trials studied smokers from the general population, 5 evaluated smokers with mental disorders, 3 studied patients with opioid or cocaine dependency, 4 studied smokeless tobacco, and 5 trials studied other patient features. [5] Roughly one-third of studies had unclear bias in sequence generation, one-third were unclear to high risk of bias for incomplete outcome data, and half of the studies had unclear allocation concealment. [5] However, the authors reported a low risk of bias for the majority of included trials. Pooled analysis found no significant difference in cardiovascular SAEs compared to placebo (RR 1.03, 95% CI 0.72–1.49; I^2=0%, p=0.9327). [5] Similarly, no significant difference in all-cause mortality was found in varenicline-treated patients versus placebo (RR 0.88, 95% CI 0.50–1.52; I^2=10.4%, p=0.3411). [5] The authors did not report sources of support for the included studies.[5]

A systematic review and meta-analysis evaluated the effectiveness of smoking cessation strategies in severe mentally ill patients.[6] Twenty-six RCTs trials were included for qualitative analysis of which 18 were pooled for meta-analysis.[6] The primary clinical outcome was self-reported smoking cessation with biochemical verification at short-term follow-up (4 weeks or less), mid-term (up to 6 months), or long-term (>6 months).[6] The majority of studies included patients with a diagnosis of schizophrenia or schizoaffective disorder, and two included patients with bipolar disorder.[6] Requirements for clinically stable symptoms or steady doses of medications widely varied or were not reported in the studies. [6] Eight pooled trials of bupropion compared to placebo showed significantly improved quit rates in the medium term (26.2% vs 8.3%, RR = 2.93 (95% CI 1.61–5.34)) and long term (16.5% vs 5%, RR = 3.04 (95% CI 1.10–8.42)). [6] The majority of trials did not find significant changes in psychiatric symptoms however adverse events were not reported in a standardized manner. [6] The authors concluded that no

significant worsening was found after smoking cessation, but results should be interpreted with caution due to the authors assessment that the included trials had an overall high risk or unclear risk of bias.[6]

A systematic review and meta-analysis examined the effectiveness of psychological, pharmacological, and combined smoking cessation interventions in patients with current depression.[7] The primary outcome was 7-day point prevalence abstinence at short term (up to 3 months) and long-term (6 months or longer) follow-up.[7] The impact of smoking cessation treatment on depression symptoms was also explored.[7] Twenty RCTs were identified (N=5,061), 14 of which involved either bupropion, varenicline, fluoxetine, or NRT. Pooled data demonstrated an overall favorable effect of pharmacotherapy vs placebo at ≤3 month follow-up (24.7 vs 19.7%, respectively; RR = 1.53 (95% CI = 1.29–1.81)) as well as the ≥6-month follow-up (19.9% vs 17.4%, respectively; RR = 1.59 (95% CI = 1.23–2.05)).[7] One trial compared the efficacy of sequential fluoxetine treatment, standard fluoxetine treatment and transdermal nicotine patch monotherapy in which point prevalence abstinence rates at 26 weeks after quitting were 40% and 15.4% and 23.5%, respectively (p=NA).[7] Nineteen of the 20 trials failed to detect a statistically significant difference in depression scores with smoking cessation treatment.[7] Due to substantial study heterogeneity and that almost half the included studies were rated as weak methodological quality, the authors could not make firm conclusions regarding the optimal smoking cessation treatment model in this population.[7]

After review, 14 systematic reviews were excluded due to poor quality, wrong study design of included trials, comparator, or outcome studied.

New Guidelines:
The National Institute for Health and Care Excellence (NICE) updated their guidelines in 2018 for brief advice, behavioral support, and pharmacotherapies for commissioners and providers of stop smoking support.[8] The following recommendations of evidence-based smoking interventions were provided:

- Ensure individual or group behavioral support is available and provided by stop smoking staff trained to the National Center for Smoking Cessation and Training (NCSCT) Standard (individual behavioral counselling) and preferably hold an appropriate counselling qualification.
- Ensure very brief advice (<30 seconds) given by frontline healthcare staff is delivered according to the NCSCT training manual on very brief advice.
- For adult smokers, prescribe bupropion, combination of short- and long-acting nicotine replacement therapy (NRT), or varenicline before they stop smoking.
    - Agree to a quit date set within the first 2 weeks of bupropion treatment and within the first 1 to 2 weeks of varenicline treatment. Reassess the person shortly before the prescription ends.
    - Agree to a quit date if NRT is prescribed. Ensure that the person has NRT ready to start the day before the quit date.
- Consider NRT for young people over 12 who are smoking and dependent on nicotine.
    - If NRT prescribed, offer it with behavioral support
- Consider text messaging as an adjunct to behavioral support

New Formulations:
None identified.

New FDA Safety Alerts:

The FDA made changes to the labeling of varenicline warning that the drug is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated. [9] The warning is based on results from a placebo-controlled study in pediatric patients that examined two weight-adjusted doses of varenicline in pediatric patients mostly 12-16 years that found its use did not significantly increase abstinence rates. [9] In addition, the FDA alert communicated that adverse effects identified during post-approval use of Chantix™ were updated on the label which included neuropsychiatric adverse events, seizures, accidental injury, cardiovascular events, somnambulism, angioedema, hypersensitivity reactions, and increased alcohol effects. [9]

A late 2016 FDA safety communication had removed black box warnings for both Chantix™ and Zyban™ labels regarding risk of serious side effects on mood, behavior, and thinking. [10] Although the risk of mental health side effects is still present, especially in those with past or current treatment for mental illness, the FDA determined that the benefits of smoking cessation outweigh the potential harms caused by the medications. [10] See **Table 1** for a summary of the FDA alerts.

Table 1. Description of New FDA Safety Alerts[9,10]

Generic Name	Brand Name	Month / Year of Change	Type of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
varenicline	Chantix™	2/2019	Product label update	Drug is not recommended for pediatric patients 16 years of age or younger because its efficacy in this population has not been demonstrated. Adverse effects identified during post-approval period included neuropsychiatric adverse events, seizures, accidental injury, cardiovascular events, somnambulism, angioedema, hypersensitivity reactions, and increased alcohol effects.
varenicline	Chantix™	12/16/2016	Removal of Boxed Warning and risk evaluation and mitigation strategy (REMS) requirement	Removed Boxed Warning for serious mental health side effects from the Chantix drug label. Removed risk evaluation and mitigation strategy (REMS) that formally required Medication Guide Added clarification that risk of serious mental health side effects is present but lower than previously suspected. Updated warning section on label that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.

Bupropion SR	Zyban™	12/16/2016	Removed language from the Boxed Warning section and risk evaluation and mitigation strategy (REMS) that required Medication Guide	Removed language describing the serious mental health side effects seen in patients quitting smoking from the Boxed Warning section. Removed risk evaluation and mitigation strategy (REMS) that formally required Medication Guide. Added clarification that risk of serious mental health side effects is present but lower than previously suspected. Updated warning section on label that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.

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Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	Route	PDL
bupropion HCl	BUPROPION HCL SR	TAB ER 12H	ORAL	Y
bupropion HCl	ZYBAN	TAB ER 12H	ORAL	Y
nicotine	NICOTINE PATCH	PATCH DYSQ	TRANSDERM	Y
nicotine	NICODERM CQ	PATCH TD24	TRANSDERM	Y
nicotine	NICOTINE	PATCH TD24	TRANSDERM	Y
nicotine	NICOTINE PATCH	PATCH TD24	TRANSDERM	Y
nicotine	NTS	PATCH TD24	TRANSDERM	Y
nicotine polacrilex	NICORELIEF	GUM	BUCCAL	Y
nicotine polacrilex	NICORETTE	GUM	BUCCAL	Y
nicotine polacrilex	NICOTINE GUM	GUM	BUCCAL	Y
nicotine polacrilex	QUIT 2	GUM	BUCCAL	Y
nicotine polacrilex	QUIT 4	GUM	BUCCAL	Y

nicotine polacrilex	COMMIT	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICORETTE	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZENGE	BUCCAL	Y
nicotine polacrilex	QUIT 2	LOZENGE	BUCCAL	Y
nicotine polacrilex	QUIT 4	LOZENGE	BUCCAL	Y
nicotine polacrilex	STOP SMOKING AID	LOZENGE	BUCCAL	Y
nicotine polacrilex	NICORETTE	LOZNG MINI	BUCCAL	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZNG MINI	BUCCAL	Y
varenicline tartrate	CHANTIX	TAB DS PK	ORAL	Y
varenicline tartrate	CHANTIX	TABLET	ORAL	Y
nicotine	NICOTROL	CARTRIDGE	INHALATION	N
nicotine	NICOTROL NS	SPRAY	NASAL	N

Appendix 2: New Comparative Clinical Trials

A total of 17 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design, comparator, or outcome studied. The remaining 9 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Baker, et al. [11] OL, RCT	Varenicline vs C-NRT (nicotine patch + nicotine lozenges) vs nicotine patch	Adult smokers (≥ 5 cpd) (n=1086)	7-day point prevalence abstinence at 26 weeks, confirmed with CO levels	Abstinence rates at 26 weeks: varenicline: 23.6% C-NRT: 26.8% Nicotine Patch: 22.8% NS for all group comparisons
Benowitz, et al.[12] DB, PC, RCT	Varenicline and bupropion vs nicotine patch or placebo	Smokers, with or without established psychiatric diagnoses (n=8058)	Time to development of a major adverse cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) during 12-week treatment	Time to development of MACE over 12 weeks varenicline: hazard ratio, 0.29; 95% CI, 0.05-1.68 bupropion: hazard ratio, 0.50; 95% CI, 0.10-2.50 NS for time to onset of MACE for either varenicline or bupropion treatment vs placebo
Eisenberg, et al.[13] DB, PC, RCT	Varenicline vs placebo	Adult smokers hospitalized with acute	7-day point-prevalence smoking abstinence assessed at 24 weeks confirmed with CO levels	Abstinence rates at 24 weeks varenicline: 47.3% placebo: 32.5% RD 14.8; 95% CI 3.9 to 25.8; p=0.012

		coronary syndrome (n=302)		
Nanovskaya, et al.[14] DB, PC, RCT	Bupropion SR vs placebo	Adult pregnant female smokers (n=65)	7-day point-prevalence smoking abstinence assessed at 12 weeks and at end of pregnancy confirmed by CO levels; symptom relief during treatment	Abstinence rates at 12 weeks bupropion:17% placebo: 3% P=0.087 Abstinence rates at end of pregnancy bupropion:10% placebo: 3% P=0.328 NS findings between groups for total nicotine withdrawal symptoms and tobacco cravings (P=0.068 and 0.08, respectively)
Tulloch, et al. [15] OL, RCT	NRT (nicotine patches) vs. Extended NRT (high-dose nicotine patches plus nicotine gum or inhalers ad libitum) vs. varenicline	Adult smokers (≥10 cpd) (n=737)	Continuous abstinence rate during weeks 5–52 confirmed by CO levels	Abstinence rates for weeks 5-52 NRT: 10% Extended NRT: 12.4% varenicline: 15.3% P>0.025 NS for group comparisons
Smith, et al.[16] DB, PC, RCT	Varenicline vs. placebo	Adult smokers (≥6 cpd) with schizophrenia or schizoaffective disorder on antipsychotic therapy and RBANS scores <90 (n=91)	Change in cognitive performance as assessed by the MATRICS Consensus Cognitive Battery by week 8 of drug treatment.	Change from baseline in MATRICS Battery Scores by week 8: Varenicline: -0.19 +/- 2.14 Placebo: +1.67 +/- 1.86 NS (p=0.511)

Rose, et al.[17] DB, PC, RCT	Varenicline + bupropion vs. varenicline + placebo	Adult male smokers (CPD ≥10) stratified based on previous response to NRT (n=174)	Number of participants completing continuous 4-week smoking abstinence at weeks 8–11 after the target quit date confirmed by CO levels.	Overall abstinence rates at weeks 8-11 for NRT non-responders Varenicline + bupropion: 42% Varenicline + placebo: 41% p-value not reported Overall abstinence rates at weeks 8-11 for NRT responders Varenicline + bupropion: 56% Varenicline + placebo: 51% p-value not reported
Foa, et al.[18] RCT, DB, DP	Varenicline and smoking cessation counseling (VARCC) + prolonged exposure (PE) therapy vs VARCC only	Adults with nicotine dependence and PTSD (n=142)	7-day point prevalence abstinence post-treatment at 3 and 6 months verified by CO levels	Abstinence rates at 3 months: VARCC + PE: 20% VARCC only: 6% (p=NS) Abstinence rates at 6 months: VARCC + PE: 9.8% VARCC only: 1.8% (p=NS)
Murphy, et al.[19] RCT, QB, DP	NRT patch vs. varenicline for smoking cessation	Adult smokers with substance use disorder (SUD) (n=110)	7 -day smoking cessation at 1 and 3 months confirmed by expired alveolar CO levels of < 10 ppm or salivary cotinine < 16 ng/ml	Abstinence rates at 1 month: Varenicline: 10% NRT: 18% (NS) Abstinence rates at 3 months: Varenicline: 15% NRT: 4% (NS)

Abbreviations: CO=carbon monoxide; CPD=cigarettes per day; C-NRT=combination nicotine replacement therapy; DB=double blind; DP=Double Placebo; HIS=Heaviness of Smoking Index; MATRICS=Measurement and Treatment Research to Improve Cognition in Schizophrenia; NRT=nicotine replacement therapy; NS = Non-significant; OR=odds ratio; OL=open-label; PC=placebo controlled; PTSD=post-traumatic stress disorder; QB=quadruple blind; RCT=randomized clinical trial; RBANS=Repeatable Battery For The Assessment Of Neuropsychological Status; SUD=substance use disorder

Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial
Baker TB, Piper, ME, Stein, JH, Smith, S, Bolt, DM, Fraser, DL, Fiore, MC.

IMPORTANCE: Smoking cessation medications are routinely used in health care; it is vital to identify medications that most effectively treat this leading cause of preventable mortality., OBJECTIVE: To compare the efficacies of varenicline, combination nicotine replacement therapy (C-NRT), and the nicotine patch for 26-week quit rates., DESIGN, SETTING, AND PARTICIPANTS: Three-group randomized intention-to-treat clinical trial occurring from May 2012 to November 2015 among smokers recruited in the Madison, Wisconsin, and Milwaukee, Wisconsin, communities; 65.5% of smokers offered the study (2687/4102) refused participation prior to randomization., INTERVENTIONS: Participants were randomized to one of three 12-week open-label smoking cessation pharmacotherapy groups: (1) nicotine patch only (n = 241); (2) varenicline only (including 1 prequit week; n = 424); and (3) C-NRT (nicotine patch + nicotine lozenge; n = 421). Six counseling sessions were offered., MAIN OUTCOMES AND MEASURES: The primary outcome was carbon monoxide-confirmed self-reported 7-day point-prevalence abstinence at 26 weeks. Secondary outcomes were carbon monoxide-confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52., RESULTS: Among 1086 smokers randomized (52% women; 67% white; mean age, 48 years; mean of 17 cigarettes smoked per day), 917 (84%) provided 12-month follow-up data. Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including point-prevalence abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, the risk differences for abstinence were, for patch vs varenicline, -0.76% (95% CI, -7.4% to 5.9%); for patch vs C-NRT, -4.0% (95% CI, -10.8% to 2.8%); and for varenicline vs C-NRT, -3.3% (95% CI, -9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion., CONCLUSIONS AND RELEVANCE: Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 weeks. The results raise questions about the relative effectiveness of intense smoking pharmacotherapies.

Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial
Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM.

Importance: Quitting smoking is enhanced by the use of pharmacotherapies, but concerns have been raised regarding the cardiovascular safety of such medications. Objective: To compare the relative cardiovascular safety risk of smoking cessation treatments. Design, Setting, and Participants: A double-blind, randomized, triple-dummy, placebo- and active-controlled trial (Evaluating Adverse Events in a Global Smoking Cessation Study [EAGLES]) and its nontreatment extension trial was conducted at 140 multinational centers. Smokers, with or without established psychiatric diagnoses, who received at least 1 dose of study medication (n = 8058), as well as a subset of those who completed 12 weeks of treatment plus 12 weeks of follow up and agreed to be followed up for an additional 28 weeks (n = 4595), were included. Interventions: Varenicline, 1 mg twice daily; bupropion hydrochloride, 150 mg twice daily; and nicotine replacement therapy, 21-mg/d patch with tapering. Main Outcomes and Measures: The primary end point was the time to development of a major adverse cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) during treatment; secondary end points were the occurrence of MACE and other pertinent cardiovascular events (MACE+: MACE or new-onset or worsening peripheral vascular disease requiring intervention, coronary revascularization, or hospitalization for unstable angina). Results: Of the 8058 participants, 3553 (44.1%) were male (mean [SD] age, 46.5 [12.3] years). The incidence of cardiovascular events during treatment and follow-up was low (<0.5% for MACE; <0.8% for MACE+) and did not differ significantly by treatment.

No significant treatment differences were observed in time to cardiovascular events, blood pressure, or heart rate. There was no significant difference in time to onset of MACE for either varenicline or bupropion treatment vs placebo (varenicline: hazard ratio, 0.29; 95% CI, 0.05-1.68 and bupropion: hazard ratio, 0.50; 95% CI, 0.10-2.50). Conclusions and Relevance: No evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment was observed. The findings of EAGLES and its extension trial provide further evidence that smoking cessation medications do not increase the risk of serious cardiovascular events in the general population of smokers.

Varenicline for Smoking Cessation in Hospitalized Patients With Acute Coronary Syndrome

Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, Cassavar D, Dion D, Haught H, Mehta SR, Baril JF, Lambert C, Madan M, Abramson BL, Dehghani P, Evita Investigators.

BACKGROUND: Less than one-third of smokers hospitalized with an acute coronary syndrome (ACS) remain abstinent following discharge. We assessed whether varenicline, begun in-hospital, is efficacious for smoking cessation following ACS. METHODS AND RESULTS: We conducted a multi-center, double-blind, randomized, placebo-controlled trial in which smokers hospitalized with an ACS were randomized to varenicline or placebo for 12 weeks. All patients received low-intensity counseling. The primary end point was point-prevalence smoking abstinence assessed at 24 weeks by 7-day recall and biochemical validation using expired carbon monoxide. A total of 302 patients were randomized (mean age 55+/-9 years; 75% male; 56% ST-segment elevation myocardial infarction; 38% non-ST-segment elevation myocardial infarction; 6% unstable angina). Patients smoked a mean of 21+/-11 cigarettes/d at the time of hospitalization and had been smoking for a mean of 36+/-12 years. At 24 weeks, patients randomized to varenicline had significantly higher rates of smoking abstinence and reduction than patients randomized to placebo. Point-prevalence abstinence rates were 47.3% in the varenicline group and 32.5% in the placebo group (P=0.012; number needed to treat=6.8). Continuous abstinence rates were 35.8% and 25.8%, respectively (P=0.081; number needed to treat=10.0), and rates of reduction >/=50% in daily cigarette consumption were 67.4% and 55.6%, respectively (P=0.05; number needed to treat=8.5). Adverse event rates within 30 days of study drug discontinuation were similar between groups (serious adverse events: varenicline 11.9%, placebo 11.3%; major adverse cardiovascular events: varenicline 4.0%, placebo 4.6%). CONCLUSIONS: Varenicline, initiated in-hospital following ACS, is efficacious for smoking cessation. Future studies are needed to establish safety in these patients.

Bupropion sustained release for pregnant smokers: a randomized, placebo-controlled trial
Nanovskaya TN, Oncken C, Fokina VM, Feinn RS, Clark SM, West H, Jain SK, Ahmed MS, Hankins GDV.

BACKGROUND: Bupropion is used to treat depression during pregnancy. However, its usefulness as a smoking cessation aid for pregnant women is not fully known. OBJECTIVE: The objective of the study was to evaluate the preliminary efficacy of bupropion sustained release for smoking cessation during pregnancy. STUDY DESIGN: We conducted a randomized, prospective, double-blind, placebo-controlled, pilot trial. Pregnant women who smoked daily received individualized behavior counseling and were randomly assigned to a 12 week, twice-a-day treatment with 150 mg bupropion sustained release or placebo. The primary study objectives were to determine whether bupropion sustained release reduces nicotine withdrawal symptoms on the quit date and during the treatment period compared with placebo and whether it increases 7 day point prevalence abstinence at the end of the treatment period and at the end of pregnancy. RESULTS: Subjects in the bupropion (n = 30) and placebo (n = 35) groups were comparable in age, smoking history, number of daily smoked cigarettes, and nicotine dependence. After controlling for maternal age and race, bupropion sustained release reduced cigarette cravings (1.5 +/- 1.1 vs 2.1 +/- 1.2, P = .02) and total nicotine withdrawal symptoms (3.8 +/- 4.3 vs 5.4 +/- 5.1, P = .028) during the treatment period. Administration of bupropion sustained release reduced tobacco exposure, as determined by levels of carbon monoxide in exhaled air (7.4 +/- 6.4 vs 9.1 +/- 5.8, P = .053) and concentrations of cotinine

in urine (348 +/- 384 ng/mL vs 831 +/- 727 ng/mL, P = .007) and increased overall abstinence rates during treatment (19% vs 2%, P = .003). However, there was no significant difference in 7 day point prevalence abstinence rates between the 2 groups at the end of medication treatment (17% vs 3%, P = .087) and at the end of pregnancy (10% vs 3%, P = .328). CONCLUSION: Individual smoking cessation counseling along with the twice-daily use of 150 mg bupropion sustained release increased smoking cessation rates and reduced cravings and total nicotine withdrawal symptoms during the treatment period. However, there was no significant difference in abstinence rates between groups at the end of medication treatment and at the end of pregnancy, likely because of the small sample size. A larger study is needed to confirm these findings and to examine the potential benefit/ risk ratio of bupropion sustained release for smoking cessation during pregnancy.

Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial
Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD.

BACKGROUND: Extended use of combined pharmacotherapies to treat tobacco dependence may increase smoking abstinence; few studies have examined their effectiveness. The objective of this study was to evaluate smoking abstinence with standard nicotine patch (NRT), extended use of combined formulations of nicotine replacement therapy (NRT+), or varenicline (VR)., METHODS: A total of 737 smokers, including those with medical and psychiatric comorbidities, were randomly assigned to one of the above three treatment conditions. The NRT group received 10 weeks of patches (21 mg daily maximum); the NRT+ group received patches (35 mg daily maximum) and gum or inhaler for up to 22 weeks; and the VR group received 1 mg twice daily for up to 24 weeks (22 weeks post target quit date). All participants also received six standardized 15-minute smoking cessation counseling sessions by nurses experienced in tobacco dependence treatment. The primary outcome was carbon monoxide-confirmed continuous abstinence rates (CAR) from weeks 5-52. Secondary outcomes were: CAR from weeks 5-10 and 5-22, and carbon monoxide-confirmed 7-day point prevalence (7PP) at weeks 10, 22, and 52. Adjusted and unadjusted logistic regression analyses were conducted using intention-to-treat procedures., RESULTS: The CARs for weeks 5-52 were 10.0 %, 12.4 %, and 15.3 % in the NRT, NRT+, and VR groups, respectively; no group differences were observed. Results with 7PP showed that VR was superior to NRT at week 52 (odds ratio (OR), 1.84; 97.5 % Confidence Interval (CI), 1.04-3.26) in the adjusted intention-to-treat analysis. Those in the VR group had higher CAR at weeks 5-22 (OR, 2.01; CI, 1.20-3.36) than those in the NRT group. Results with 7PP revealed that both NRT+ (OR, 1.72; CI, 1.04-2.85) and VR (OR, 1.96; CI, 1.20-3.23) were more effective than NRT at 22 weeks. As compared to NRT monotherapy, NRT+ and VR produced significant increases in CAR for weeks 5-10 (OR, 1.52; CI, 1.00-2.30 and OR, 1.58; CI, 1.04-2.39, respectively); results were similar, but somewhat stronger, when 7PP was used at 10 weeks (OR, 1.57; CI, 1.03-2.41 and OR, 1.79; CI, 1.17-2.73, respectively). All medications were well tolerated, but participants in the VR group experienced more fatigue, digestive symptoms (e.g., nausea, diarrhea), and sleep-related concerns (e.g., abnormal dreams, insomnia), but less dermatologic symptoms than those in the NRT or NRT+ groups. The frequency of serious adverse events did not differ between groups., CONCLUSIONS: Flexible and combination NRT and varenicline enhance success in the early phases of quitting. Varenicline improves abstinence in the medium term; however, there is no clear evidence that either varenicline or flexible, dual-form NRT increase quit rates in the long-term when compared to NRT monotherapy.

Varenicline Effects on Smoking, Cognition, and Psychiatric Symptoms in Schizophrenia: A Double-Blind Randomized Trial
Smith RC, Amiaz R, Si TM, Maayan L, Jin H, Boules S, Sershen H, Li C, Ren J, Liu Y, Youseff M, Lajtha A, Guidotti A, Weiser M, Davis, JM.

Schizophrenic patients have a high rate of smoking and cognitive deficits which may be related to a decreased number or responsiveness of nicotinic receptors in their brains. Varenicline is a partial nicotinic agonist which is effective as an antismoking drug in cigarette smokers, although concerns have been raised about potential psychiatric side-effects. We conducted a double-blind placebo controlled study in 87 schizophrenic smokers to evaluate the effects of varenicline (2 mg/day) on measures of smoking, cognition, psychiatric symptoms, and side-effects in schizophrenic patients who were cigarette smokers. Varenicline

significantly decreased cotinine levels (P<0.001), and other objective and subjective measures of smoking (P < .01), and responses on a smoking urges scale (P = .02), more than placebo. Varenicline did not improve scores on a cognitive battery designed to test the effect of drugs on cognitive performance in schizophrenia (the MATRICS battery), either in overall MATRICS battery Composite or individual Domain scores, more than placebo. There were no significant differences between varenicline vs. placebo effects on total symptom scores on psychiatric rating scales, PANSS, SANS, or Calgary Depression scales, and there were no significant drug effects in any of these scales sub-scores when we used Benjamin-Hochberg corrected significance levels (alpha = .05). Varenicline patients did not show greater side-effects than placebo treated patients at any time point when controlled for baseline side-effect scores. Our study supports the use of varenicline as a safe drug for smoking reduction in schizophrenia but not as a cognitive enhancer.

Combination Varenicline/Bupropion Treatment Benefits Highly Dependent Smokers in an Adaptive Smoking Cessation Paradigm
Rose JE, Behm FM.

Introduction: This study replicated and extended results of a previous trial, which found that combination varenicline/bupropion treatment increased smoking abstinence in smokers who were male, highly dependent, and who did not respond to prequit nicotine patch treatment with a >50% reduction in expired-air carbon monoxide in the first week., Methods: One hundred and twenty-two male nicotine patch nonresponders and 52 responders were identified. Smokers in each group were randomized to receive 12 weeks of varenicline plus bupropion treatment versus varenicline plus placebo. The primary outcome was continuous smoking abstinence at weeks 8-11 after the target quit date., Results: For smokers with a high level of dependence, judged by having a baseline Fagerstrom Test for Nicotine Dependence (FTND) score >= 6 and cigarette consumption >= 20/d, combination varenicline/bupropion treatment increased the abstinence rate relative to varenicline alone: 71.0% versus 43.8% (odds ratio = 3.14; 95% confidence interval = 1.11-8.92, p [one tailed] = .016). In contrast, less dependent smokers did not show a benefit of combination treatment relative to varenicline (abstinence rates of 32.1% vs. 45.6%, respectively); there was a significant interaction of treatment and dependence level. Patch nonresponders tended to benefit the most from combination treatment, which was well tolerated overall., Conclusions: Combination varenicline/bupropion treatment proved significantly more efficacious than varenicline alone among highly dependent male smokers. These results, together with prior studies, support an adaptive treatment paradigm that assigns smoking cessation treatment according to baseline smoker characteristics and initial response to nicotine patch treatment., Implications: This study replicated, in a prospective manner, an important and surprising retrospective finding from a previous clinical trial, which showed that a specific subpopulation of smokers benefited substantially from receiving a combination treatment of varenicline plus bupropion, relative to varenicline plus placebo. Specifically, male smokers having high baseline nicotine dependence (FTND score >= 6 and cigarette consumption >= 20/d), showed a marked increase in smoking abstinence rate on combination pharmacotherapy. The present study likewise found an enhancement in end-of-treatment abstinence rate in this subgroup, from 43.8% to 71.0%. The adaptive treatment paradigm, which classifies smokers based on initial dependence level and response to prequit nicotine patch treatment, may be used to identify target populations of smokers whose success can be enhanced by intervening with combination pharmacotherapy before the quit-smoking date.

Concurrent varenicline and prolonged exposure for patients with nicotine dependence and PTSD: A randomized controlled trial
Foa EB, Asnaani A, Rosenfield D, Zandberg LJ, Gariti P, Imms P.

BACKGROUND: Prevalence of smoking among individuals with posttraumatic stress disorder (PTSD) is disproportionately high, and PTSD is associated with especially poor response to smoking cessation treatment., OBJECTIVE: The current study examined whether integrating treatments for smoking cessation (varenicline plus smoking cessation counseling; VARCC) and PTSD (prolonged exposure therapy; PE) enhances smoking outcomes among smokers diagnosed with PTSD., METHOD: 142 adults with nicotine dependence (ND) and PTSD were randomized to a treatment program consisting of varenicline, smoking cessation counseling, and PE (VARCC + PE) or to VARCC only. Seven-day point prevalence abstinence (PPA) at posttreatment (3-months postquit day) and follow-up (6-

months postquit day), verified by serum cotinine levels and exhaled carbon monoxide, was the primary smoking outcome. Psychological outcomes were PTSD and depression severity. Mixed effects models included baseline PTSD severity as a moderator of treatment condition effects., RESULTS: Overall, VARCC + PE participants did not show greater PPA than VARCC participants. However, treatment effects were moderated by baseline PTSD severity. For participants with moderate and high PTSD severity, VARCC + PE led to significantly higher PPA than VARCC alone (ps<.05). No differences between treatment conditions emerged for participants with low baseline PTSD severity. Participants who received PE showed significantly greater reduction of PTSD and depression symptoms than those who did not receive PE., CONCLUSIONS: Integrating psychological treatment for PTSD and smoking cessation treatment enhances smoking cessation for participants with moderate or severe PTSD symptom severity, but does not enhance smoking cessation for participants with low baseline PTSD severity.

Effects of varenicline versus transdermal nicotine replacement therapy on cigarette demand on quit day in individuals with substance use disorders
Murphy CM, MacKillop J, Martin RA,Tidey JW, Colby SM, Rohsenow DJ.

RATIONALE: Cigarette demand is a behavioral economic measure of the relative value of cigarettes. Decreasing the value of cigarette reinforcement may help with quitting smoking., OBJECTIVES: This study aimed to evaluate the effects of initial use of varenicline (VAR) versus nicotine replacement therapy (NRT) on demand for cigarettes on quit day among smokers with substance use disorders (SUD) and to determine whether reduced demand was associated with subsequent abstinence from smoking at 1 and 3 months., METHODS: Participants (N = 110) were randomized to double-blind, double-placebo conditions: VAR with placebo NRT or NRT with placebo capsules. The cigarette purchase task (CPT) was used to assess demand for cigarettes at baseline and on quit day, following a 1-week medication dose run-up/placebo capsule lead-in and first day use of the patch., RESULTS: Demand for cigarettes decreased from baseline to quit day without significant differences between medications. Reductions in CPT intensity (number of cigarettes that would be smoked if they were free) and CPT breakpoint (lowest price at which no cigarettes would be purchased) predicted greater likelihood of abstaining on quit day. Reduced intensity predicted length of abstinence at 1 and 3 months while reduced breakpoint predicted only 1 month length of abstinence., CONCLUSIONS: Initial therapeutic doses of VAR and NRT resulted in similar reductions in cigarette reinforcement. Larger initial reductions in demand on quit day were associated with early success with abstaining from cigarettes. Behavioral economic approaches may be useful for identifying individuals who benefit less from pharmacotherapy and may need additional treatment resources.,

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 5 2019
1 nicotinic agonists.mp. or Nicotinic Agonists/7477
2 tobacco cessation products.mp./7
3 nicotine replacement.mp./2815
4 smoking cessation.mp. or Smoking Cessation/33408
5 "tobacco use disorder".mp. or "Tobacco Use Disorder"/10776
6 nicotine gum.mp./638
7 nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/1633
8 nicotine patch.mp. or "Tobacco Use Cessation Devices"/2268
9 nicoderm.mp./25
10 nicotine spray.mp./39
11 bupropion.mp. or Bupropion/4289
12 varenicline.mp. or Varenicline/1527

13 1 or 2 or 3 or 6 or 7 or 8 or 9 or 10 or 11 or 12/14687
14 4 or 5/39341
15 13 and 14/5943
16 limit 15 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) 297
17 from 16 keep 1, 5, 8, 16-17, 33, 35.../62
18 from 17 keep 1-2, 4-7, 11, 13-21, 24-25, 27-33.../45
19 from 18 keep 1-2, 4-7, 9-36, 38-45 /42
20 from 19 keep 1-4, 6-14, 16-19, 21-27, 29-42 /38
21 nicotinic agonists.mp. or Nicotinic Agonists/7477
22 tobacco cessation products.mp. /7
23 nicotine replacement.mp./ 2815
24 smoking cessation.mp. or Smoking Cessation/33408
25 "tobacco use disorder".mp. or "Tobacco Use Disorder"/10776
26 nicotine gum.mp. /638
27 nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/1633
28 nicotine patch.mp. or "Tobacco Use Cessation Devices"/2268
29 nicoderm.mp./25
30 nicotine spray.mp./39
31 bupropion.mp. or Bupropion/4289
32 varenicline.mp. or Varenicline/ 1527
33 21 or 22 or 23 or 26 or 27 or 28 or 29 or 30 or 31 or 32/14687
34 24 or 25/39341
35 33 and 34/5943
36 limit 35 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))/297
37 from 36 keep 1, 5, 8, 16-17, 33, 35.../62
38 from 37 keep 1-2, 4-7, 11, 13-21, 24-25, 27-33.../45
39 from 38 keep 1-2, 4-7, 9-36, 38-45 /42
40 from 39 keep 1-4, 6-14, 16-17, 19-27, 29-42 /38

Appendix 5: Key Inclusion Criteria

Population	Patients with tobacco use disorder
Intervention	Pharmacotherapy (nicotine replacement: patches, gum, lozenges, nasal spray, inhalation cartridges); bupropion, or varenicline with or without behavioral therapy
Comparator	Placebo or active comparator
Outcomes	Point prevalence abstinence/smoking cessation
Timing	Any study duration; literature search from July 2016 to July 2019
Setting	Inpatient hospital or outpatient clinics; worldwide

Smoking Cessation

Goal(s):

- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products

Length of Authorization:

- 3-6 months

Requires PA:

- Non-preferred drugs
- Nicotine replacement therapy (NRT) for more than 6 months in the absence of behavioral counseling
- Varenicline treatment for more than 12 weeks

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis for tobacco dependence (ICD10 F17200)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a preferred NRT product?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5	**No:** Go to #8
5. Is the patient at least 17 years of age?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has patient quit?	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Go to #7
7. Is the patient enrolled in a smoking cessation behavioral counseling program [e.g. Quit Line at: 800-QUIT-NOW (800-784-8669)].	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Pass to RPh. Deny; medical appropriateness
8. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA for initial treatment. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve treatment for up to 6 months

P&T Review: *9/19 (DE); 7/16; 4/12*
Implementation: *8/16, 7/23/12*

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Drug Class Literature Scan: Drugs for Duchenne Muscular Dystrophy

Date of Review: September 2019

Date of Last Review: July 2017
Literature Search: 01/01/17 – 06/14/19

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- Two high-quality systematic reviews were identified which evaluated pharmacologic treatment for Duchenne muscular dystrophy (DMD).[1,2]
- Current evidence demonstrates no difference in functional outcomes for eteplirsen compared to placebo.[1,2] Evidence is significantly limited by high risk of bias and small sample sizes. There is no new clinical efficacy or safety evidence that would change current policy for eteplirsen.
- Deflazacort received an expanded FDA approval for children from 2 to 5 years of age.[3] Labeling was also updated to recommend administration of all routine immunizations prior to initiation of treatment with deflazacort.[3]

Recommendations:
- Update prior authorization (PA) criteria to include updated FDA-approved ages and assessment of immunization status prior to initiation of treatment with deflazacort.

Summary of Prior Reviews and Current Policy
- Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 7250 males between the ages of 5 to 24 years.[4] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death before the age of 20.[5] Only 25% of patients remain ambulatory by age 16.[6]
- There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology currently recommend either deflazacort or prednisone as first-line treatment in children to improve muscle and pulmonary function and reduce risk of scoliosis.[5,7]
- Therapies FDA approved for treatment of DMD were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in July 2017 and include eteplirsen and deflazacort. A previous evaluation of deflazacort found insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions. Evidence was limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients. An evaluation of eteplirsen found insufficient evidence that eteplirsen is associated with any clinical change in symptoms or functional status for patients with DMD.

Author: Sarah Servid, PharmD

- Prior authorization (PA) is currently required for eteplirsen and deflazacort to ensure medically appropriate use (see **Appendix 1**). Prednisone is available without PA.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A 2017 drug review conducted by the OHSU Drug Effectiveness Review Project assessed evidence for eteplirsen efficacy and safety.[1] Evidence included 3 poor quality phase 1/2 trials of eteplirsen administered intramuscularly (n=7) or intravenously (n=31).[1] Early phase 1/2 trials demonstrated no consistent significant dose response in dystrophin expression or the North Star Ambulatory Assessment for muscle function.[1] Randomized, placebo-controlled data is limited to 12 patients administered eteplirsen 30 or 50 mg/kg over 24 weeks.[1] After 24 weeks, all patients entered an open-label treatment phase. Outcomes included the 6-minute walk test and level of dystrophin production evaluated via muscle biopsy. At 24 weeks, there was no significant difference in the 6-minute walk test between placebo and eteplirsen.[1] Results for dystrophin production upon biopsy were conflicting depending on the method of analysis. Randomized data was significantly limited by differences in baseline characteristics between groups and variable outcome assessment measures.[1] Open-label, uncontrolled data was further limited by use of a historical control as a comparator and risk for motivation bias and coaching which can bias outcomes in favor of treatment.[1]

Because initial analysis of dystrophin positive fibers by western blot were oversaturated and uninterpretable, the manufacturer worked with the FDA to improve analyses for dystrophin production.[1] Repeat biopsies at week 180 were analyzed by western blot (which evaluates amount of dystrophin) and immunohistochemistry (which evaluates localization of dystrophin in tissue).[1] Western blot analyses demonstrated an average dystrophin level that was 0.93% of the normal protein level in healthy patients and immunohistochemistry analyses demonstrated that number of muscle fibers producing any dystrophin was increased from 1.1% at baseline to 17.4% at Week 180.[1] Dystrophin analyses were significantly limited by collection of 180-week biopsies from different muscle sites, lack of baseline values, and storage of control samples for 3 years with risk for protein degradation prior to analysis.[1] Due to these limitations, FDA medical reviewers concluded that dystrophin production was not interpretable as a categorically different result.[1]

Similar results were noted in a high quality systematic review and meta-analysis which examined effect of exon skipping drugs on functional outcomes (6-minute walk test and North Star Ambulatory Assessment) in patients with DMD.[2] The systematic review identified only a single trial of eteplirsen compared to placebo.[2] Overall, authors concluded that there is no evidence that exon-skipping drugs are effective in DMD based on currently available data.[2]

After review, 2 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[8,9]

New Guidelines:
No new high quality guidelines were identified.

New Formulations and Indications:
No new formulations were identified.

Since initial approval, deflazacort has received an expanded indication in patients 2 to 5 years of age.[3] It was previously approved in patients at least 5 years of age, and this expanded approval was based on efficacy and safety in patients 5 years and older with DMD.[3]

New FDA Safety Labeling:
Labeling for deflazacort was updated to recommend administration of all routine immunizations prior to initiation of treatment with deflazacort. Live-attenuated or live vaccines should be administered at least 4 to 6 weeks prior to starting therapy.[3]

Randomized Controlled Trials
A total of 8 citations were manually reviewed from the initial literature search. After further review, all studies were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10-14]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
deflazacort	EMFLAZA	PO	ORAL SUSP	
deflazacort	EMFLAZA	PO	TABLET	
eteplirsen	EOXNDYS 51	IV	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 2 2019

1	deflazacort.mp.	505
2	eteplirsen.mp.	78
3	exp Muscular Dystrophies/	25480
4	1 or 2	582
5	3 and 4	161
6	limit 5 to (english language and humans)	143
7	limit 6 to yr="2017 -Current"	48
8	limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	8

Appendix 3: Key Inclusion Criteria

Population	Patients with DMD
Intervention	Deflazacort or eteplirsen
Comparator	Other active comparators or placebo
Outcomes	Symptom, disability or functional improvement Mechanical ventilation Disease progression Morbidity or mortality
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Drugs for Duchenne Muscular Dystrophy

Goal(s):

- Encourage use of corticosteroids which have demonstrated long-term efficacy
- Restrict use of eteplirsen and deflazacort to patients with Duchenne Muscular Dystrophy and limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids

Length of Authorization:

- 6 months

Requires PA:

Eteplirsen (billed as a pharmacy or physician administered claim)
Deflazacort

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the drug being used to treat an OHP-funded condition AND is the requested treatment funded by the OHP for that condition? Note: Treatments referenced on an unfunded line of the prioritized list (http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Prioritized-List.aspx) are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Note: Eteplirsen and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
4. Is the request for continuation of eteplirsen treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #9~~8~~
6. Is the patient ≥ ~~5~~ 2 years of age?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, measles, mumps, rubella, and varicella.	**Yes:** Go to #8 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort?	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of another oral corticosteroid.
9. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: • Deletion of exons 45 to 50 • Deletion of exons 48 to 50 • Deletion of exons 49 and 50 • Deletion of exon 50 OR • Deletion of exon 52?	**Yes:** Go to #10~~9~~ Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
10. Has the patient been on a stable dose of corticosteroid for at least 6 months?	**Yes:** Go to #11~~0~~	**No:** Pass to RPh. Deny; medical appropriateness.
11. Has baseline functional assessment been evaluated using a validated tool such as the 6-minute walk test or North Star Ambulatory Assessment?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Approve for up to 6 months Document functional status.	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *09/19; 11/17; 07/17 (SS)*
Implementation: *TBD; 1/1/18; 9/1/17*

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Prior Authorization Criteria Update: Cystic Fibrosis

Purpose of Update:

1. In April 2019, the Food and Drug Administration (FDA) expanded the label of ivacaftor (Kalydeco®) for the treatment of cystic fibrosis (CF) in patients ages 6 months and older who have one mutation in the cystic fibrosis transmembrane conductance regulatory (CFTR) gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro data.[1] Previously, ivacaftor was approved in patients age 12 months and older.

   Approval is based on unpublished, low-quality data from a phase 3 open-label, 24- week safety and pharmacokinetic study including 25 children less than 24 months of age with one of ten gating mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H).[2] However, the only enrolled mutations included G551D (n=10) or G178R (n=1).[3] The study was funded by Vertex Pharmaceuticals, who had a role in study design, data collection, data analysis, data interpretation and writing of the report. Data from the first cohort of patients (age 12-24 months) has been published (n=19)[2], but data in those 6-12 months old remains unpublished (n=11).[3] The safety profile of ivacaftor 25 mg, 50 mg or 75 mg twice daily was similar to that observed in patients with CF 2 years of age and older. Only one patient experienced elevated liver transaminases, and there were no discontinuations due to adverse events.[1] Efficacy and safety from placebo-controlled trials has only been established in pediatric patients 6 years of age and older.[4] Efficacy in patients age 6 months to less than 12 months old was extrapolated from patients 6 years of age and older based on population pharmacokinetic analyses showing similar drug exposure.[1]

   The safety and efficacy of ivacaftor in patients with CF younger than 6 months of age have not been established. The use of ivacaftor in patients less than 6 months of age cannot be recommended at this time.

2. In June 2019, FDA also expanded the FDA labeling for tezacaftor/ivacaftor (Symdeko®) for the treatment of pediatric patients ages 6 years and older with CF who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[5] Previously, tezacaftor/ivacaftor was approved in patients age 12 years and older.

   Similarly, efficacy in this population was extrapolated from patients aged 12 years and older and approval was supported by a 24-week, open-label, phase 3 study designed to assess safety and pharmacokinetics (n=70).[6] The majority of patients (n=61) were homozygous for *F508del* and the remaining (n=9) were heterozygous for *F508del* with a second mutation with residual function. Patients had to weigh 15 kg or more and have a baseline percent predicated FEV_1 ($ppFEV_1$) of 40% or greater. Mean baseline $ppFEV_1$ was 91%.[6] The safety profile was observed to be similar to clinical trials in ages 12 and older, and pharmacokinetic population analysis demonstrated similar overall exposure. The most common treatment emergent adverse events were cough (35.7%), CF exacerbation (22.9%), pyrexia (18.6%) and nasal congestion (14.3%).[6] There was only one discontinuation due to an adverse event and no deaths occurred. Additionally, there was a least squares absolute change from baseline in sweat chloride of -14.5 mmol/L at week 25 (95% CI -17.4 to -11.6), but no significant effect on least squares mean absolute change in $ppFEV_1$ (0.9%; 95% CI -0.6 to 2.3).[6] This study used a weight-based dosing

regimen that differs from the FDA-approved dosing regimens for patients age 6 through 11 years. The dosing regimen in the study used a 40 kg weight-based dosing cutoff, while 30 kg is included in the FDA label.

Recommendation:

- Update prior authorization criteria to reflect recent changes in FDA approved labels for ivacaftor and tezacaftor/ivacaftor.

References:

1. KALYDECO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; April 2019
2. Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med*. 2018;6(7):545-553
3. Davies JC, Wang LT, Campbell D, et al. Ivacaftor treatment in patients 6 to <12 months old with a CFTR gating mutation: results of a Phase 3, two-part, single-arm study. Poster and abstract presented at: North American Cystic Fibrosis
4. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with *G551D* mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219–1225.
5. SYMDEKO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; June 2019.
6. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 to 11 years with cystic fibrosis. *J Cyst Fibros.* 2019:1-6. doi: 10.1016/j.jcf.2019.06.009.

Oral Cystic Fibrosis Modulators

Goals:

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- 90 days to 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)

Preferred Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #5	
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10

Approval Criteria		
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is ~~12~~ 6 months of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented mutation in the CFTR gene that ivacaftor is FDA approved for (see below)? FDA approved CFTR mutations include: E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC –T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X	**Yes:** Go to #17	**No:** Go to #9 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
9. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Go to #13

Approval Criteria		
11. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #17	**No:** Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)
13. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Does the patient have a diagnosis of cystic fibrosis and is ~~12~~ 6 years of age or older?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Go to #17	**No:** Go to #16 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.

Approval Criteria		
16. Does the patient have at least one mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and FDA labeling? Note: A list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor include: A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
17. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness
18. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #20 If unknown, these labs need to be collected prior to approval.	

Approval Criteria		
20. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days. Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on IVA (see **Renewal Criteria**). If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness
3. If the prescription is for lumacaftor/ivacaftor or tezacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.	
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 3 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

Dosage and Administration:

<u>Ivacaftor:</u>

- Adults and pediatrics age ≥6 years: 150 mg orally every 12 hours with fat-containing foods
- Children age ~~1~~ 6 months to <6 years:
  - 5 kg to less than 7 kg: 25 mg packet every 12 hours
  - 7 kg to < 14 kg: 50 mg packet every 12 hours
  - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Age ≥6 years: one 150 mg tablet once daily
    - Age 1 to < 6 years with body weight < 14 kg: 50 mg packet once daily; with body weight ≥ 14 kg : 75 mg packet of granules once daily
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **twice weekly** (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **once daily** (half of normal dose)
Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort Grapefruit Juice	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥12 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours

- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Children age 2 to <6 years:
  - < 14 kg: 1 packet (LUM 100mg/IVA125mg) every 12 hours
  - ≥ 14 kg: 1 packet (LUM 150mg/IVA 188mg) every 12 hours
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - Age ≥ 6 years: 2 tablets in the morning and 1 tablet in the evening
    - Age 2 to <6 years: 1 packet in the morning and 1 packet every other day in the evening
  - Severe impairment (Child-Pugh class C): Use with caution after weighing the risks and benefits of treatment.
    - Age ≥ 6 years: 1 tablet twice daily, or less
    - Age 2 to <6 years: 1 packet once daily, or less
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

Tezacaftor/ivacaftor:

- Adults and pediatrics age ≥~~12~~ 6 years weighing ≥30 kg : 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Pediatrics age ≥ 6 years weighing < 30 kg: TEZ 50mg/IVA 75 mg in the morning and IVA 75 mg in the evening
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
  - Severe impairment (Child-Pugh class C):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
    - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
  - When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
    - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

P&T Review: *9/19 (MH);* *9/18 ~~(MH)~~; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *11/1/2018; 1/1/16; 8/25/15; 8/12*

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Drug Class Update: Short-acting and Long-acting Opioids

Date of Review: September 2019

Date of Last Review: November 2016
End Date of Literature Search: 03/28/2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The focus of this update is to review evidence for short-acting opioids (SAOs) and long-acting opioids (LAOs) published since this drug class was last presented to the Pharmacy and Therapeutics (P&T) Committee.

Research Questions:
1. What is the comparative efficacy or effectiveness of different opioids in reducing pain and improving functional outcomes (e.g., disability) in adult patients being treated for acute or chronic non-cancer pain?
2. Do harms differ between drugs with and without abuse-deterrent mechanisms or between drugs with different abuse-deterrent mechanisms?
3. What are the comparative harms (including addiction and abuse) of different opioids in adult patients being treated for acute or chronic non-cancer pain?
4. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) with acute or chronic non-cancer pain for which one opioid is more effective or associated with less harm?

Conclusions:
- In a systematic review and meta-analysis of randomized clinical trials (RCTs) of patients with chronic non-cancer pain, high-quality evidence showed that opioid use was associated with statistically significant, but modest improvements in pain (−0.69 cm on a 10-cm pain scale; 95% confidence interval [CI] −0.82 to −0.56, P<0.001) and physical functioning (2.04 of 100 points, 95% CI 1.41 to 2.68 points on the 100-point SF-36 physical component score, P<0.001), and increased risk of vomiting (relative risk [RR] 3.44, 95% CI 2.80 to 4.10) compared with placebo.[1] Low- to moderate-quality evidence showed no difference in pain and physical functioning when opioids were compared with nonsteroidal anti-inflammatory drugs (NSAIDs) or nortriptyline.[1] Moderate-quality evidence suggested opioids were associated with greater pain relief than antiepileptic drugs (weighted mean difference [WMD] −0.90, 95% CI −1.65 to −0.14 cm on the 10-cm pain scale), but no significant differences in physical function were noted.[1]
- A high quality systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) concluded there is low to moderate quality evidence demonstrating opioids have statistically significant, but minimal effects in alleviating pain (mean difference, about 1 point on a 0- to 10-point pain scale) or improving function (mean difference, about 1 point on the 24 point Roland-Morris Disability Questionnaire) when opioids are used to treat chronic low back pain (LBP).[2] Trials included in the systematic review were not designed to assess long-term risks for overdose or opioid use disorder because of relatively small samples sizes, short follow-up, and exclusion of higher-risk patients.[2]

Author: Deanna Moretz, PharmD, BCPS

- A 2017 Cochrane review evaluated the occurrence and nature of adverse events associated with opioid medications when used to manage chronic, non-cancer pain.[3] Low to moderate quality evidence showed an increased risk of any adverse event with opioid treatment compared to placebo (absolute event rate with opioids 78% vs. absolute event rate with placebo 55%; number needed to treat for harmful outcome [NNTH] = 5; RR 1.42; 95% CI 1.22 to 1.66). [3] Similar adverse event trends were observed when opioids were compared to an active non-opioid comparator (absolute event rate with opioids 58% vs. absolute event rate with non-opioid comparator 48%; NNTH = 10; RR 1.21, 95% CI 1.10 to 1.33).[3]
- The American Society of Interventional Pain Physicians (ASIPP) 2017 Guideline provides recommendations for prescribing opioids to manage chronic non-cancer pain in adults.[4] The recommendations emphasize chronic opioid therapy should be provided only to patients with proven medical necessity and stable improvement in pain and function. Chronic opioid therapy is recommended independently or in conjunction with other modalities of treatments only at low doses with appropriate adherence monitoring and understanding of adverse events.[4]
- The updated 2017 Veterans Affairs (VA)/Department of Defense (DOD) clinical practice guideline for opioid therapy for chronic pain support the current Oregon Health Plan (OHP) prior authorization policies for short- and long-acting opioid analgesics.
- The updated VA/DoD 2017 clinical practice guideline for diagnosis and treatment of low back pain (LBP) includes a recommendation that for patients with acute or chronic LBP, the first-line pharmacologic strategy is to treat with NSAIDs, with consideration of patient-specific risks (based on high quality evidence).[5] The current literature for patients with acute LBP or acute exacerbations of chronic LBP shows insufficient evidence to support short-term (less than 7 days) opioid therapy.[5] There is high quality evidence against initiating long-term opioid therapy in patients with LBP.[5] A 2017 clinical practice guideline from the American College of Physicians (ACP) also focused on noninvasive treatments for acute, subacute, and chronic LBP.[6] Clinicians should only consider opioids as a treatment option in patients with LBP who have failed the other treatments, and only after a discussion of known risks and realistic benefits with patients if the potential benefits outweigh the risks.[6]
- In February 2019, the CDC issued key clarification on the 2016 guidance for prescribing opioids for chronic pain.[7] The statement conveys the CDC guideline is not intended to deny clinically appropriate opioid therapy to any patients who suffer acute or chronic pain from conditions such as cancer and sickle cell disease, but rather to ensure that physicians and patients consider all safe and effective treatment options for pain management with the goal of reducing inappropriate use.[7]

Significant Food and Drug Administration Safety Alerts

- As of April 2017, the Food and Drug Administration (FDA) is recommending to restrict the use of codeine and tramadol medicines in children.[8] These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. Codeine and tramadol should not be used to treat pain after tonsillectomy or adenoidectomy in children younger than 18 years.[8] Avoid use in adolescents between 12 to 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of breathing problems.[8] Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults.[8] The FDA also recommends against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.[8]
- As of January 2018 the FDA is requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older.[9] The risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death with these medicines outweigh their benefits in patients younger than 18.[9]
- In September 2018, the FDA added a REMS program requirement for all opioids.[10] The program includes continuing education for providers regarding pain management, safe dispensing, and recommended monitoring. There is no mandatory federal requirement that prescribers take training and no precondition to prescribing or dispensing opioid analgesics to patients. All opioid product labeling was updated to reflect this change. The FDA's goal is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of opioid analgesics, while maintaining patient access to pain medications.[10]

- An April 2019 FDA safety communication alerted practitioners about reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased.[11] The FDA is requiring changes to the prescribing label for these medicines that are intended for use in the outpatient setting. These changes are designed to promote safe tapering or discontinuing of opioids in patients who are physically dependent on the medication.[11]

Recommendations:

- Revise prior authorization Criteria (PA) as follows:
  - Add dihydrocodeine morphine milliequivalents to opioid conversion chart listed in SAO PA criteria
  - Add pain associated with sickle cell disease and severe burn injury as an exclusion to SAO and LAO PA criteria
  - Add concomitant benzodiazepine/CNS depressant use as an assessment to SAO and LAO PA criteria
  - Remove taper plan for patients using chronic SAO's for back and spine, based on HERC guidance
- Retire codeine PA criteria and add a question about use of codeine and tramadol to the SAO PA criteria to insure appropriate use in patients under the age of 19 years based on FDA safety alerts.
- No changes to the Preferred Drug List (PDL) are recommended based on recent evidence.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

A literature scan focused on SAOs was presented to the P and T Committee in May 2015. Recommendations from the review were to update current PA criteria for excessive dose limits on opioid/non-narcotic combination products based on FDA labeling. Propoxyphene products and combination products containing 500 mg of acetaminophen were removed from the Preferred Drug List (PDL), and the maximum recommended daily aspirin dose was decreased from 8 gram per day to 4 gram per day.

The purpose of November 2016 opioid analgesic class update was to propose new drug policies for SAOs and LAOs that aligned with guidance from the CDC and the prioritized list of health services established by the Oregon Health Plan (OHP) Health Evidence Review Commission (HERC). Prior authorization criteria for opioid analgesics approved by the P&T Committee at the November 2016 meeting are outlined in **Appendix 5**. Specific recommendations included:

- Maintain non-preferred status for Troxyca ER (oxycodone/naltrexone) extended-release capsules.
- Patients with a terminal diagnosis or cancer diagnosis are exempt from PA.
- All non-preferred SAO products and preferred SAO products prescribed for more than 7 days are subject to clinical PA criteria.
- All long-acting opioid analgesics are subject to clinical PA criteria.

Most of the Fee for Service (FFS) utilization in the first quarter of 2019 for LAOs was for preferred agents (extended release morphine extended release and fentanyl patches). The majority of the 2019 first quarter utilization for the SAOs included the preferred products, hydrocodone/acetaminophen, oxycodone and tramadol.

At the May 16, 2019 Value-based Benefits Subcommittee (VbBS) meeting of the Health Evidence Review Commission (HERC) the members explored expansion of coverage and treatments for 5 chronic pain conditions that were currently unfunded on the Oregon Health Authority (OHA) Prioritized List of Health Services.[12] An independent external review of the evidence was completed by Aggregate Analytics Incorporated. The conditions specified in the HERC proposal included

fibromyalgia, chronic pain syndrome, chronic pain due to trauma, other chronic post-procedural pain, and other chronic pain. Pharmacologic interventions included opioids and non-opioid therapies. Non-pharmacologic interventions included tai chi, yoga, exercise, acupuncture, interdisciplinary rehabilitation, mindfulness, massage, physical therapy, cognitive behavioral therapy and education. The VbBS recommended to not reprioritize chronic pain syndrome, fibromyalgia and related conditions due to lack of evidence of effectiveness of available treatment modalities and to consider readdressing the prioritization of these conditions as part of the 2022 or 2024 Biennial Review.[12] This recommendation was approved by HERC members at their May 16, 2019 committee meeting and no changes were made to the OHA Prioritized List.[13] In addition wording for Guideline Note 60, which outlines when opioids are covered for back and neck conditions, was revised to state: "For patients receiving long-term opioid therapy (>90 days) for conditions of the back and spine, continued coverage of opioid medications requires an individual treatment plan which includes a taper plan *when clinically indicated*."[13] This recommendation was approved by the HERC members and will be effective October 1, 2109.[13]

Background:

To estimate the prevalence of chronic pain in the United States (U.S.), the CDC analyzed 2016 National Health Interview survey (NHI) data.[14] The NHI survey is a cross-sectional, in-person, household health survey of the civilian noninstitutionalized U.S. population, conducted by the National Center for Health Statistics (NCHS).[14] Results from the survey revealed an estimated 20.4% (50.0 million) of U.S. adults had chronic pain and 8.0% of U.S. adults (19.6 million) had high-impact chronic pain (i.e., chronic pain that frequently limits life or work activities).[14] Higher prevalences of both chronic pain and high-impact chronic pain were reported among women, older adults, adults living in poverty, adults with public health insurance, and rural residents.[14] Among adults less than 65 years, the age-adjusted prevalence of chronic pain was higher among those with Medicaid and other public health care coverage or other insurance (e.g., Veteran's Administration, certain local and state governments) than among adults with private insurance or those who were uninsured.[14] Among adults aged 65 years and greater, those with both Medicare and Medicaid had higher age-adjusted prevalence of chronic pain than did adults with all other types of coverage.[14]

Although opioids are commonly prescribed for pain, opioids have shown modest efficacy in pain reduction.[15] Evidence supports short-term efficacy (less than 12 weeks) of opioids for relieving pain and improving function in non-cancer nociceptive and neuropathic pain, although the effects in some pain conditions such as low back pain are modest and may not be clinically meaningful for most patients.[15] Evidence for long-term efficacy of opioids is lacking despite well documented risks for long-term opioid therapy.[16] Opioid analgesics are widely diverted and improperly used, which has resulted in a national epidemic of opioid-related deaths.[17] Unintentional drug overdose death rates increased from 4.0 per 100,000 in 1999 to 17.1 in 2016 ($p<0.05$).[18] In 2016, a total of 17,087 persons in the United States died from drug overdoses involving prescription opioids.[18] The FDA issued an alert regarding safety issues associated with concomitant use of opioids with drugs that depress the central nervous system (CNS) in 2016.[19] An FDA review found combined use of opioid medicines with benzodiazepines or other CNS depressants has resulted in serious side effects, including slowed or difficult breathing and deaths.[19]

Because of these alarming trends, in 2016 the CDC issued guidance for prescribing opioids to serve as a resource to providers treating adults with chronic pain outside of active cancer treatment, palliative care, or end-of-life care.[15] The CDC recommended opioids only be initiated for treatment of chronic non-cancer pain when alternative therapies have not provided sufficient pain relief or cannot be used (e.g., contraindications to non-opioid analgesics) **and** pain is adversely affecting a patient's function and/or quality of life **and** when the potential benefits of opioid therapy outweigh potential harms **and** after discussion with the patient of all risks, benefits, and alternatives to opioid therapy.[15] The CDC guidance is based on a systematic review of studies over the past 20 years, expert opinion and stakeholder review.[15] To encourage uptake of the guideline, CDC developed a comprehensive implementation plan. In addition, CDC has developed clinical decision support tools that health care systems can incorporate into clinical workflow within electronic health records.

According to data compiled by the CDC, healthcare providers wrote 72.4 opioid prescriptions per 100 persons in 2006.[18] This rate increased annually by 3.0% from 2006 to 2010, decreased 1.6% annually from 2010 to 2014, and continued to decrease annually by 8.2% until 2017, reaching a rate of 58.5 prescriptions per 100 persons.[18] This represents an overall relative reduction of 19.2% from 2006 to 2017.[18] Between 2006 and 2017, the annual prescribing rate for high dosage opioid prescriptions (≥ 90 morphine milligram equivalents/day) decreased from 11.5 to 5.0 prescriptions per 100 persons, an overall relative reduction of 56.5%.[18] The proportion of opioid prescriptions that were high dosage declined from 15.9% in 2006 to 8.5% in 2017.[18] Although some prescribing practices continued to improve in 2017, sustained efforts are needed to help providers adopt and maintain safe prescribing behaviors.[18]

In 2019, an American Academy of Pain Medicine (AAPM) consensus panel report identified challenges with implementing the 2016 CDC guidance.[20] The AAPM panel largely supported the CDC opioid guideline, but noted challenges for providers with respect to application of opioid dosage ceilings and prescription duration guidance, failure to appreciate the importance of patient involvement in decisions to taper or discontinue opioids, barriers to diagnosis and treatment of opioid use disorder, and impeded access to recommended comprehensive, multimodal pain care.[20] In February 2019, the CDC issued key clarification on the 2016 guidance for prescribing opioids for chronic pain.[7] The clarification letter was addressed to The American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the National Comprehensive Cancer Network® (NCCN). The letter conveys the CDC guideline is not intended to deny clinically appropriate opioid therapy to any patients who suffer acute or chronic pain from conditions such as cancer and sickle cell disease, but rather to ensure that physicians and patients consider all safe and effective treatment options for pain management with the goal of reducing inappropriate use.[7] In April 2019 the FDA issued a safety warning regarding reports of serious harm in patients physically dependent on opioid pain medications who were discontinued or had rapid dose reductions in opioid therapy.[21] Reported harms included serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. The FDA has required label changes in opioid medications to guide prescribers on gradual, individualized tapering of opioids.[21] A variety of factors, including the dose of the drug, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient should be considered when tapering opioids.[21] No standard opioid tapering schedule exists that is suitable for all patients.[21]

Pain intensity measurements used in clinical trials include the visual analog scale (VAS; scale, 0-100 or 0-10) and numerical rating scale (NRS; scale, 0-10).[22] The NRS and VAS are highly correlated and can be interpreted equally. For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[23] Similar MCID values have been shown with 100-point scales.[24] The proposed MCID thresholds for chronic pain and low back pain are about 2.0 points on the 0 to 10-point scale or 20 points on the 0 to 100-point scale.[22] The impact of opioids on disability is also frequently studied in clinical trials of low back pain. Measurements commonly used include the Oswestry Disability Index scores (range, 0-100) and the Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[22] The Oswestry Disability Index and RMDQ tools are also highly correlated and share similar properties.[22] Similarly, a 10-point difference in 0-100 scales for chronic disability is considered a “minimal” difference and 20-point differences are considered to be “clinically important”.[22]

The Brief Pain Inventory (BPI) is widely used in pain specialty and research settings, but is impractical for clinicians caring for patients in the office due to instrument length and scoring complexity.[25] An ultra-brief pain measure derived from the BPI was developed and validated in patients with chronic pain in 2009.[25] This 3-item scale assesses pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) using a VAS ranging from 0 (no pain/no interference) to 10 (pain as bad as you imagine/complete interference).[25] The PEG scale proved to be a reliable and valid measure of pain among primary care patients with chronic musculoskeletal pain and diverse Veterans Affairs (VA) ambulatory patients.[25] The PEG was also comparable to the BPI in terms of responsiveness to between patients with and without pain improvement at 6 months.[25] For these reasons, the PEG scale was added to the OHP PA criteria for opioids in 2016.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Opioids for Chronic Non-cancer Pain

A high quality systematic review and meta-analysis included evidence published through April 2018 to evaluate safety and efficacy of opioids for management of chronic non-cancer pain.[1] The primary outcomes were pain intensity (score range, 0-10 cm on a VAS for pain; lower is better with a MCID of 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MCID is 5 points), and incidence of vomiting.[1] Trials that met inclusion criteria randomized patients to an oral or transdermal opioid versus any non-opioid control and conducted follow-up for at least 4 weeks. Ninety-six RCTs including 26,169 subjects were identified.[1] Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain.[1] There were 9 RCTs that reported no industry funding, 76 RCTs that reported receiving industry funding, and 11 RCTs that did not specify funding type.[1] All trials were at risk of bias for at least 1 of the methodological domains; however, 53% of trials adequately generated their randomization sequence, 50% adequately concealed allocation, 88% blinded patients, 88% blinded caregivers, 87% blinded data collectors, and 85% blinded outcome assessors.[1] There were 73 trials (76%) with frequent (≥20%) missing outcome data.[1]

High-quality evidence from 42 RCTs that followed patients for 3 months or longer found that opioids were associated with reduced pain versus placebo (WMD −0.69 cm, 95% CI −0.82 to −0.56 cm on a 10-cm VAS for pain, P<0.001); although the difference did not reach the MCID of 1 cm.[1] High-quality evidence from 51 RCTs showed opioids were associated with a small improvement in physical functioning compared with placebo, but did not meet the criterion for the MCID of 5 points (WMD 2.04 points, 95% CI 1.41 to 2.68 points on the 100-point SF-36 physical component score, P<0.001).[1] High quality evidence from 51 RCTs showed opioids were associated with an increased incidence of vomiting compared to placebo (RR 3.44, 95% CI 2.80 to 4.10).[1] Compared with placebo, opioids were associated with increased drowsiness, constipation, dizziness, nausea, dry mouth, and pruritus.[1]

Moderate-quality evidence from 9 RCTs showed no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief (WMD −0.60 cm, 95% CI −1.54 to 0.34 cm on the 10-cm VAS for pain, P=0.21).[1] Moderate-quality evidence from 7 RCTs suggested no difference in physical functioning between opioids and NSAIDs (WMD −0.90 points, 95% CI −2.69 to 0.89 points on the 100-point SF-36 physical component score, P=0.33).[1] High-quality evidence from 5 RCTs showed an association of opioids with vomiting compared with NSAIDs (RR 4.71, 95% CI 2.92 to 7.60, P<0.001; risk difference 6.3%, 95% CI 3.2% to 11.1%).[1]

Low-quality evidence from 3 RCTs suggested no difference in pain relief between opioids and nortriptyline (WMD −0.13 cm, 95% CI −0.99 to 0.74 cm) on the 10-cm VAS for pain, P=0.78).[1] Low-quality evidence from 2 trials suggested no difference in physical functioning (WMD −5.31 points, 95% CI −13.77 to 3.14 points on

the 100-point SF-36 physical component score, P=0.22).[1] Moderate-quality evidence from 3 RCTs suggested opioids were associated with greater pain relief than antiepileptic drugs (WMD −0.90 cm, 95% CI −1.65 to −0.14 cm on the 10-cm VAS for pain, P=0.02, MCID 1 cm).[1] Low-quality evidence suggested no difference in physical functioning (WMD 0.45 points, 95% CI −5.77 to 6.66 points on the 100-point SF-36 physical component score).[1]

In this meta-analysis of RCTs of patients with chronic non-cancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but modest improvements in pain and physical functioning, and increased risk of vomiting compared with placebo.[1] Comparisons of opioids with NSAIDs and nortriptyline suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.[1] Moderate-quality evidence suggested opioids were associated with greater pain relief than antiepileptic drugs, but no significant differences in physical function were noted.[1] No trial followed patients for more than 6 months, so it was not possible to assess long-term safety and efficacy of opioids from this analysis.[1] In addition, trials of opioid therapy for chronic non-cancer pain excluded patients with current or prior substance use disorders or other active mental illness, so there is insufficient evidence to assess opioid safety or efficacy in these subpopulations.[1]

Pharmacologic Therapies for Low Back Pain

A high quality systematic review funded by the AHRQ evaluated current evidence on systemic pharmacologic therapies for acute or chronic low back pain.[2] This systematic review was subsequently used by the American College of Physicians (ACP) to update a clinical practice guideline on managing low back pain.[6] The literature search included evidence published from January 2007 through November 2016. The review focused on adults with non-radicular or radicular low back pain of any duration categorized as acute (< 4 weeks), subacute (4 to 12 weeks), and chronic (≥ 12 weeks).[2] Outcomes were long-term (≥1 year) or short-term (≤6 months) pain, function, and harms. Treatments included acetaminophen, NSAIDs, opioids, tramadol and tapentadol, antidepressants, skeletal muscle relaxants, benzodiazepines, corticosteroids, and antiepileptic drugs versus placebo, no treatment, or other therapies.[2] The strength of evidence for pain and function was graded as moderate quality.[2] Methodological shortcomings included high attrition (30% to 60% in most trials), short follow-up (maximum of 16 weeks) and use of an enriched enrollment randomized withdrawal design by some trials.[2] An enriched enrollment randomized withdrawal (EERW) design excludes potential participants who are non-responders or who cannot tolerate the experimental drug before random assignment which may bias efficacy results with regard to magnitude of effect.[26] However, in a comparison between EERW and non-EERW opioid trials for chronic pain, the authors found the EERW trial design did not appear to bias the results of efficacy, but it could underestimate the adverse effect reporting.[26]

Thirty-eight publications evaluated opioids, tramadol, or tapentadol versus placebo or other treatments in management of low back pain.[2] For acute low back pain, 1 trial found no difference between oxycodone or acetaminophen plus naproxen (n = 108) and placebo plus naproxen (n = 107) in pain or function.[2] For chronic low back pain, 1 systematic review found that opioids (morphine, oxymorphone, hydromorphone, and tapentadol) were associated with greater short-term relief than placebo for pain (6 trials: standardized mean difference [SMD] -0.43, 95% CI -0.52 to -0.33, mean difference, about 1 point on a 0- to 10-point pain scale) and function (4 trials: SMD -0.26, 95% CI -0.37 to -0.15, mean difference, about 1 point on the RMDQ).[2] Tramadol also resulted in greater short-term relief than placebo for pain (5 trials: SMD -0.55, 95% CI -0.66 to -0.44, mean difference, ≤1 point on a 0- to 10-point pain scale) and function (5 trials: SMD -0.18, 95% CI -0.29 to -0.07, mean difference, about 1 point on the RMDQ).[2] Three trials reported inconsistent effects of opioids versus NSAIDs for pain relief; 1 of the trials found no difference in function.[2] Opioids had a higher risk for nausea, dizziness, constipation, vomiting, somnolence, and dry mouth than placebo.[2] Four trials found no clear differences among various long-acting opioids in pain or function.[2] Six trials found no clear differences between long- and short-acting opioids in alleviating pain.[2] Although some trials found long-acting opioids associated with greater pain relief, patients randomly assigned to these drugs also received higher doses.[2]

In summary, evidence remains is limited to short-term trials showing small effects for opioids in treating chronic low back pain; trials were not designed to assess serious harms.[2] Although head-to-head comparisons were limited, no clear differences between different long-acting opioids, or long-acting versus short-acting opioids were identified.[2] In addition, the evidence was too inconsistent to determine the effects of opioids versus NSAIDS.[2] Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow-up, and exclusion of higher-risk patients.[2]

Adverse Events Associated with Use of Opioids

A 2017 Cochrane review analyzed data from previous Cochrane meta-analyses to provide an overview of the occurrence and nature of adverse events associated with any opioid medication when used to manage chronic, non-cancer pain.[3] A total of 14 reviews presented quantitative data that investigated different opioid agents administered for time periods of two weeks or longer.[3] The opioids included in the trials were buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol. Opioid therapy was compared to placebo or non-opioid comparators including celecoxib, desimpramine, diclofenac, gabapentin, lorazepam, naproxen, and nortriptyline. The longest study was 13 months in duration, with most trials conducted over 6 to 16 weeks.[3] The quality of the included reviews was high using AMSTAR criteria, with 11 reviews meeting all 10 criteria, and 5 of the reviews meeting 9 out of 10 criteria.[3] The quality of the evidence for the adverse event outcomes according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool[27] ranged from very low to moderate.[3]

There was an increased risk of experiencing any adverse event with opioids compared to placebo (absolute event rate with opioids 78% vs. absolute event rate with placebo 55%; NNTH = 5; RR 1.42; 95% CI 1.22 to 1.66).[3] Similar adverse event trends were observed when opioids were compared to an active non-opioid comparator (absolute event rate with opioids 58% vs. absolute event rate with non-opioid comparator 48%; NNTH = 10; RR 1.21, 95% CI 1.10 to 1.33).[3] There was also a significantly increased risk of experiencing a serious adverse event with opioids compared to placebo (absolute event rate with opioids 7.5% vs. absolute event rate with placebo 4%; NNTH = 29; RR 2.75, 95% CI 2.06 to 3.67).[3] The risk of participants withdrawing from the trials due to adverse events was significantly increased with opioid treatment compared to placebo (absolute event rate with opioids 25% vs. absolute event rate with placebo 7%; NNTH = 6; RR 3.40, 95% CI 3.02 to 3.82).[3]

Significantly increased risk ratios were found with opioids compared to placebo for a number of specific adverse events: constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting.[3] There was no data reported for the following adverse events of interest in any of the included reviews: addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine dysfunction, respiratory depression, sexual dysfunction, and sleep apnea or sleep-disordered breathing.[3] No data was identified for adverse events analyzed by sex or ethnicity.[3]

Abuse-Deterrent Formulations of Opioids

The Institute for Clinical and Economic Review (ICER) published a systematic review in 2017 that assessed the effectiveness and value of ADFs of opioids.[28] This review was initiated because a 2015 FDA recommendation encouraged manufacturers to produce ADFs of opioids to reduce opioid abuse and misuse.[29] Nine extended release (ER) opioids and one immediate release (IR) opioid have FDA approved labeling describing a variety of abuse-deterrent properties.[28] A summary of FDA-approved ADF products is presented in **Table 1**. Abuse-deterrent formulations are relatively new, branded therapies for treating pain, and are generally more expensive than both their non-ADF branded equivalents and generic versions.[28] The only generic ADF on the market is an extended-release oxycodone formulation.

Table 1. Opioid Products with FDA-Approved Abuse-Deterrent Labeling[28]

Brand Name	Generic Name	Year of Approval	Abuse-Deterrence Mechanism
OxyContin®	Oxycodone	2010	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.
Embeda®	Morphine	2014	Capsules of ER morphine pellets that contain a sequestered core of naltrexone; if the pellets are swallowed, the morphine is gradually released and absorbed, while the naltrexone core passes through the gut intact. If the pellets are crushed, chewed, or dissolved, the naltrexone is released, blocking morphine-induced euphoria.
Targiniq™ ER	Oxycodone	2014	Combination pill containing ER oxycodone and naloxone; if the formulation is crushed and administered intravenously or intranasally, high naloxone concentrations block opiate-induced euphoria and can induce withdrawal symptoms.
Hysingla™ ER	Hydrocodone	2015	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.
MorphaBond®	Morphine	2015	Formulated with inactive ingredients that make the tablet harder to adulterate while maintaining ER characteristics if the tablet is subjected to physical manipulation or chemical extraction
Xtampza™ ER	Oxycodone	2016	Capsules containing microspheres formulated with oxycodone base and inactive ingredients that make the formulation harder to manipulate
Troxyca™ ER	Oxycodone	2016	Contains pellets that consist of oxycodone that surround sequestered naltrexone. When taken orally, the naltrexone is intended to remain sequestered and patients receive ER oxycodone. When the pellets are crushed, the naltrexone is released and counteracts the effects of oxycodone.
Arymo™ ER	Morphine	2017	A polymer matrix tablet technology with controlled-release properties as well as physical and chemical barriers that resist manipulation. The technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe.
Vantrela™ ER	Hydrocodone	2017	Incorporates abuse-deterrent technology designed to resist drug extraction through the most common routes: oral, intranasal, and intravenous.
RoxyBond®	Oxycodone	2017	Includes inactive ingredients that make the tablets harder to misuse by physical manipulation, chemical extraction, or both; in vitro data suggest physicochemical properties that are expected to make abuse through injection difficult. ** Only ADF approved as immediate-release formulation. **

Abbreviations: ADF = abuse-deterrent formulation; ER = extended release; FDA = Food Drug Administration

To evaluate the clinical effectiveness of ADFs, the authors abstracted evidence from available clinical and observational studies, whether in published, unpublished, or abstract form.[28] The focus was on evidence on the effects of ADFs on abuse potential endpoints (e.g., VAS measures of drug liking, take drug again), as well as real world outcomes (e.g., abuse and misuse, addiction, overdose, drug diversion).[28] In total, 41 references were identified, of which 15 were premarket RCTs that evaluated abuse potential endpoints in healthy, non-dependent recreational drug users, and 26 were post-market observational studies that primarily evaluated the real-world impact of ADFs on levels of abuse and misuse.[28]

The pre-market trials were divided into two categories: those that assessed oral abuse potential and those that assessed intranasal abuse potential. Key measures of abuse potential included maximum levels of "drug liking" ("at this moment, my liking for this drug is…"), which was a primary endpoint in the studies of focus, as well as secondary endpoints of "overall drug liking" (typically measured at 12 and 24 hours post-dose), and "take drug again" ("I would take this drug again" measured at 12 and 24 hours post-dose).[28] Drug liking endpoints were measured using a bipolar 0 to 100 mm VAS, in which 0 represents "strong disliking", 50 represents a neutral response, and 100 represents "strong liking". Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100, where 0 represents "definitely would not take drug again" and 100 represents "definitely would take drug again."[28] Of note,

there is no established threshold for what constitutes a clinically-important difference in any of these endpoints, so the clinical significance of these findings remains unclear even if statistical differences were noted.[28]

Relative to non-ADF comparators, both crushed and intact forms of each extended-release ADF produced lower scores for drug liking.[28] Drug liking in oral abuse potential studies ranged from a 7-point difference between crushed Arymo™ ER and crushed morphine sulfate ER to a 25-point difference between Hysingla™ ER and hydrocodone immediate-release (IR) solution.[28] Similarly, the incremental difference in drug liking varied across intranasal abuse potential studies, ranging from seven points (crushed Vantrela™ ER vs. hydrocodone powder) to 36 points (crushed Targiniq™ ER vs. oxycodone IR powder).[28] Crushed versions of each ADF generally produced higher drug liking scores than intact oral versions, but both remained lower than non-ADF comparators.[28] The use of these surrogate outcomes (measures of drug liking, take drug again, etc.) in the abuse potential premarket studies of an ADF constitutes an important source of uncertainty concerning the effectiveness of ADFs.[28]

Twenty-six post-market studies evaluated real-world evidence on the impact of ADFs on abuse and misuse outcomes; all were non-randomized studies focusing exclusively on OxyContin® and comparators.[28] Comparators were either prescription opioids (e.g. IR oxycodone, extended release [ER] morphine) or illicit drugs (e.g. heroin).[28] The time frames varied from evaluating pre-reformulation years (2008 to 2010) compared with post-reformulation years (2011 to 2014).The majority of studies found that after the abuse-deterrent formulation of OxyContin® was introduced in 2010, there was a decline in the rate of OxyContin® abuse ranging from 12% to 75% in different study populations and at different post-reformulation time points.[28] However, the non-oral route of abuse declined at a significantly greater rate compared with the oral route of abuse, suggesting there may have been a shift from non-oral routes to the oral route of abuse.[28] Many of the studies also found a contemporaneous increase in the rate of abuse of other prescription opioids (ER oxymorphone, ER morphine, IR oxycodone) and heroin during the same periods examined.[28] Limited evidence indicates that rates of overdose and overdose deaths attributed to OxyContin® declined after its abuse-deterrent formulation was introduced, with decreases ranging between 34% and 65%.[28] No prospective studies conducted in cohorts that measured real-world incidence of abuse among ADF and non-ADF users were identified.[28] Instead, the current evidence of real-world impact is limited to time series, which are subject to potential confounding factors and other biases.[28] In summary, there is insufficient evidence with which to judge the effectiveness of ADF opioids in preventing abuse, misuse, or overdose of opioids.[28]

After review, 11 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[30-41]

New Guidelines:

High Quality Guidelines

American Society of Interventional Pain Physicians Guidelines

The ASIPP 2017 Guidelines provide recommendations for the prescribing of opioids for the management of chronic non-cancer pain in adults.[4] The multidisciplinary panel composition included clinical practitioners, patients, patient surrogates, and members of the general public.[4] The guideline preparation committee and the writing of the guidelines were entirely supported financially by ASIPP and developed without any involvement from industry.[4] Conflicts of interests for panel members due to consulting, speaking, or research support are clearly presented in the guideline publication. Panel members with potential conflicts were recused from related discussion or preparation of the guidelines and these members agreed not to discuss any aspect of the guidelines with industry before data publication.[4] Strength of evidence was graded using the GRADE method[27] and recommendations were stratified into Levels 1 through 4.[4] Level 1 is supported by strong or significant evidence, with high confidence that the available evidence reflects the true magnitude and direction of the net effect and further research is very unlikely to change either the magnitude or direction to this net effect.[4] Level 2 is supported by moderate or intermediate evidence

with moderate confidence that the available evidence reflects the true magnitude and direction of the net effect.[4] Recommendations with Level 3, 4 or 5 (fair to consensus based) evidence are not included in this update. The following recommendations were graded as Level 1 or 2 based on strong to moderate quality evidence.[4]

Initial Steps of Opioid Therapy

- Utilize prescription drug monitoring programs (PDMPs) to evaluate patterns of prescription usage. (Evidence: Level I-II; Strength of Recommendation: Moderate to strong)[4]
- Establish appropriate physical diagnosis and psychological diagnosis if available. (Evidence: Level I; Strength of Recommendation: Strong)[4]
- Establish medical necessity based on average moderate to severe (≥ 4 on a scale of 0 – 10) pain and/or disability. (Evidence: Level II; Strength of Recommendation: Moderate)[4]
- Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: Level I-II; Strength of Recommendation: Moderate)[4]
- Stratification of patients based on risk of substance abuse, misuse or addiction into high risk, medium risk, and low risk is crucial in initiation and maintenance of opioid therapy. (Evidence: Level I-II; Strength of Recommendation: Moderate)[4]

Assessment of Effectiveness of Long-Term Opioid Therapy

- Clinicians must assess improvement based on analgesia, activity, aberrant behavior, and adverse effects, and clinicians must document at least 30% improvement in pain or disability without adverse consequences to establish effectiveness. (Evidence: Level II; Strength of Recommendation: Moderate)[4]
- Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring. (Evidence: Level II; Strength of Recommendation: Moderate)
- Avoid long-acting opioids for the initiation of opioid therapy. (Evidence: Level I; Strength of Recommendation: Strong)[4]
- Consider up to 40 morphine milligram equivalents (MME) as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose. (Evidence: Level II; Strength of Recommendation: Moderate)[4]
- Recommend methadone only after failure of other opioid therapy, only when prescribed by clinicians with specific training in its risks and uses, and only within FDA recommended doses. (Evidence: Level I; Strength of Recommendation: Strong)[4]
- Periodically reassess for pain relief and/or functional status improvement of ≥ 30% without adverse consequences. (Evidence: Level II; Strength of recommendation: Moderate)[4]
- Understand and educate the patients of the effectiveness and adverse consequences. (Evidence: Level I; Strength of Recommendation: Strong)
- The evidence of effectiveness is similar for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids. (Evidence: Level I-II; Strength of recommendation: Moderate to strong)[4]
- Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain that is not amenable to short-acting opioids or moderate doses of long acting opioids. (Evidence: Level I; Strength of Recommendation: Strong)[4]

Monitoring for Adherence and Side Effects

- Monitor for adherence, abuse, and noncompliance by urine drug testing (UDT) and PDMPs. (Evidence: Level I-II; Strength of Recommendation: Moderate to Strong)[4]
- Recommended methadone monitoring includes an electrocardiogram prior to initiation, at 30 days, with dose adjustments, prescription of concomitant medications that may affect QTC interval, and yearly thereafter. (Evidence: Level I; Strength of Recommendation: Strong)[4]
- Monitor for side effects including constipation and manage them appropriately, including discontinuation of opioids when indicated. (Evidence: Level I; Strength of Recommendation: Strong)[4]

Department of Veterans Affairs/Department of Defense – Chronic Pain

The updated VA/DoD 2017 clinical practice guideline for opioid therapy for chronic pain included evidence reviewed through December 2016.[42] The recommendations are based on a systematic review of both clinical and epidemiological evidence.[42] Developed by a panel of multidisciplinary experts, it provides a clear explanation of the relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.[42] The recommendations were made using a systematic approach considering four domains as per the GRADE approach.[27] These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient or provider values and preferences, and other implications, as appropriate (e.g., resource use, equity, acceptability).[42] Strong recommendations include:

Initiation and Continuation of Opioids

- Recommend against initiation of long-term opioid therapy for chronic pain. Alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments are preferred. When pharmacologic therapies are used, recommend non-opioids over opioids. (Strong recommendation)[42]
- If prescribing opioid therapy for patients with chronic pain, recommend a short duration. Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits. (Strong recommendation)[42]
- For patients currently on long-term opioid therapy, recommend ongoing risk mitigation strategies, assessment for opioid use disorder, and consideration for tapering when risks exceed benefits. (Strong recommendation)[42]
- Recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering. (Strong recommendation)[42]
- Recommend against the concurrent use of benzodiazepines and opioids. For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate. (Strong recommendation)[42]
- Recommend against long-term opioid therapy for patients less than 30 years of age due to higher risk of opioid use disorder and overdose. (Strong recommendation)[42]

Risk Mitigation

- Strongly recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies.[42] The strategies and their frequency should be commensurate with risk factors and include:
  - Ongoing, random urine drug testing (including appropriate confirmatory testing)
  - Checking state prescription drug monitoring programs
  - Monitoring for overdose potential and suicidality
  - Providing overdose education
  - Prescribing of naloxone rescue and accompanying education
- Recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months. (Strong recommendation)[42]

Type, Dose, Follow-Up and Taper of Opioids

- If prescribing opioids, recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids. (Strong recommendation)[42]

- As opioid dosage and risk increase, recommend more frequent monitoring for adverse events including opioid use disorder and overdose. Risks for opioid use disorder start at any dose and increase in a dose dependent manner. Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose. (Strong recommendation)[42]
- Recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate and consider tapering to a reduced dose or to discontinuation. (Strong recommendation)[42]
- Recommend tapering to reduce dose or to discontinue long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Abrupt discontinuation should be avoided unless required for immediate safety concerns. (Strong recommendation)[42]

Department of Veterans Affairs/Department of Defense – Low Back Pain

The updated VA/DoD 2017 clinical practice guideline for diagnosis and treatment of LBP includes evidence reviewed through October 2016.[5] Similar to the VA/DOD opioids for chronic pain recommendations, the LBP guidelines were updated by a panel of experts and patients. A systematic review of the literature was conducted and the evidence was graded by task force members using the GRADE tool.[5] The draft of the initial revisions was sent out for peer review and comments before final publication. Specific pharmacologic recommendations include:

- For patients with acute or chronic LBP, the first-line pharmacologic recommendation based on strong evidence is to treat with NSAIDs, with consideration of patient-specific risks.[5]
- The benefit of duloxetine for chronic LBP in terms of both pain and function improvement is small as demonstrated by moderate to high quality evidence.[5]
- Moderate evidence supports offering a non-benzodiazepine muscle relaxant for acute LBP. The benefits of skeletal muscle relaxants were demonstrated in two SRs, although the evidence indicates benefit is limited to short-term use of three to seven days.[5]
- In regard to long-term use, there is no evidence to suggest benefit for the use of skeletal muscle relaxants for chronic LBP.[5]
- There is insufficient evidence to support the use of benzodiazepines for acute LBP; the evidence in chronic LBP is less conclusive.[5] There is low quality data indicating that the harms/burden of benzodiazepine use outweigh the benefits.[5]
- While the current literature for patients with acute LBP or acute exacerbations of chronic LBP shows insufficient evidence to support time-limited (less than seven days) opioid therapy, on average, the potential harms of short-term opioid therapy (less than six months) outweigh the potential benefits in patients with LBP.[5] Given the significant risks and potential benefits of opioid therapy, patients should be evaluated individually, including consideration of psychosocial risks and alternative non-opioid treatments.[5]Any opioid therapy should be kept to the shortest duration and lowest dose possible.[5]
- For patients with LBP, there is strong evidence **against** initiating long-term opioid therapy.[5]
- For patients with acute or chronic LBP, there is insufficient evidence to recommend for or against the use of time-limited (less than seven days) acetaminophen therapy.[5]
- For the treatment of acute or chronic LBP, including patients with both radicular and non-radicular LBP, there is insufficient evidence to recommend for or against the use of anti-epileptics including gabapentin and pregabalin.[5]

American College of Physicians

A 2017 clinical practice guideline from the American College of Physicians (ACP) is focused on noninvasive treatments for acute, subacute, and chronic back pain.[6] The recommendations are based on a systematic review conducted by the AHRQ's Pacific Northwest Evidence-Based Practice Center previously described in this update.[2] The quality of evidence was based on the GRADE model using low, moderate, and high ratings.[27] The recommendations are as follows:

Recommendation 1:

Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select non-pharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation).[6]

Recommendation 2:

For patients with chronic low back pain, clinicians and patients should initially select non-pharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation).[6]

Recommendation 3:

In patients with chronic low back pain who have had an inadequate response to non-pharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence).[6]

Additional Guidelines for Clinical Context:

United States Department of Health and Human Services

The Comprehensive Addiction and Recovery Act (CARA) of 2016 led to the creation of the Pain Management Best Practices Inter-Agency Task Force, whose mandate is to identify gaps, inconsistencies, and updates in the available evidence and to make recommendations for best practices for managing acute and chronic pain.[43] The task force consists of 29 experts who have significant experience across the disciplines of pain management, patient advocacy, substance use disorders, mental health, and minority health.[43] The utility of the 2016 Guideline for Prescribing Opioids for Chronic Pain released by the CDC and its contribution to mitigating unnecessary opioid exposure and the adverse outcomes associated with opioids was acknowledged by the task force.[43] However, the task force also recognized unintended consequences have resulted following the release of the guidelines in 2016, which are due in part to misapplication or misinterpretation of the guideline, including forced tapers and patient abandonment.[43]

Task Force recommendations are focused on effective pain management, particularly for chronic pain, which is best achieved using a patient-centered, multidisciplinary, multimodal, integrated approach that may include pharmacotherapy.[43] In general, two broad categories of medications are used for pain management: opioids and a variety of non-opioid classes of medications.[43] Non-opioid medications that are commonly used include acetaminophen, NSAIDs, antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs] and tricyclic antidepressants [TCAs]), anticonvulsants, musculoskeletal agents, and anxiolytics.[43] The choice of medication should be based on the pain diagnosis, the mechanisms of pain, and related co-morbidities following a thorough history, physical exam, other relevant diagnostic procedures and a risk-benefit assessment that demonstrates that the benefits of a medication outweigh the risks.[43]

A special populations section of the report highlights unique issues in managing pain for children, women, older adults, pregnant women, racial and ethnic minority populations, active duty soldiers/veterans, patients with sickle cell disease or other chronic relapsing conditions, and patients with cancer. Specific recommendations for special populations include:

- Encourage and assist pain physicians in obtaining the necessary training for credentialing in pediatric pain. This is a significant step toward improving pediatric patient access. Develop pediatric pain management guidelines that address appropriate indications for opioids and responsible opioid prescribing.[43]

- Develop pain management guidelines for older adults that address their unique risk factors. However, a risk factor of a medication should not necessarily be an automatic reason not to give this medication to an elderly patient. Clinicians must assess the risk versus benefit of using medications while considering other modalities in this patient population.[43]
- Increase research to elucidate further understanding of the mechanisms driving sex differences in pain responses and research of mechanism-based therapies that address those differences. Raise awareness in the public and health care arenas to the unique challenges that women face during pregnancy and in the postpartum period, including various pain syndromes and psychosocial comorbidities.[43]
- Provide referrals to a comprehensive pain program early in the course of the chronic disease (e.g., sickle cell disease, multiple sclerosis, porphyria, systemic lupus erythematosus, migraine, Parkinson's disease, neuropathic pain syndromes) to determine the optimal approach to managing acute or chronic pain exacerbations, including potential non-opioid, alternative therapies and non-pharmacologic therapies. Establish a partnership between the disease specialist (e.g., the hematologist, oncologist, neurologist, or rheumatologist) and the pain team to optimize care.[43]
- Develop intervention programs informed by the biopsychosocial model to reduce racial and ethnic disparities in pain. Develop biopsychosocial interventions for pain that are scalable and culturally enhanced.[43]
- Physicians and clinical health care providers taking care of military service members and veterans, regardless of practice setting, should consider in their pain care plan prior military history and service related health factors that may contribute to acute or chronic pain, as relevant to the clinical presentation. Conduct research to better understand the biopsychosocial factors that contribute to acute and chronic pain in active duty service members and veterans, with a focus on traumatic brain injury, post-traumatic stress disorder, other mental health issues, and substance use disorders.[43]

<u>Oregon Health Authority Chronic Opioid Prescribing Guidelines</u>

The OHA recruited a task force of Oregon-based practitioners to consider endorsement of the 2016 CDC pain guidelines as the foundation for opioid prescribing in Oregon.[44] A brief addendum was created to address Oregon-specific concerns.[44] The task force relied upon on expert review from the varied organizational perspectives to develop the additional recommendations.[44] The methods used to develop the Oregon-specific recommendations are not described in the publication. Specific recommendations endorsed by the Oregon Pain Management Task Force include:

- Clinicians should strongly consider additional evaluation of the benefits and risks of higher dose opioid therapy, document clinical justification for the higher dose in the medical record, and obtain and document pain management consultation. Options for consultation could include:
    1) Having a colleague evaluate the patient
    2) Presenting and discussing the case to a clinician peer group or multi-disciplinary pain consultation team
    3) Referring the patient to a pain specialist who has experience tapering patients off opioids
    4) Referring the patient to a pain/addictions mental health specialist
- Health care professional should refer to Oregon Medical Board Material Risk Notice (required in Oregon when prescribing opioids for chronic pain.) Material Risk Notice is a written record documenting the provider-patient discussion on long-term controlled substance therapy for intractable pain.
- Task force members emphasized the need for compassionate and nondiscriminatory treatment for established (including transferred) patients currently taking higher opioid doses, echoing specific suggestions found in the CDC Guideline narrative supporting this recommendation.
- The Oregon Prescription Drug Monitoring Program (PDMP) is a tool to help health care providers and pharmacists provide patients better care in managing their prescriptions. Inappropriate behavior identified through the PDMP should lead to discussions about opioid use disorder, but not usually lead to dismissal from practice. While opioids may need to be discontinued, treatment of addiction and other medical comorbidities is still important.

- Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation above) and should consider involving pharmacists, pain specialists and/or mental health specialists as part of the management team when opioids are co-prescribed with other central nervous system depressants.
- If clinicians suspect their patient might be sharing or selling opioids and not taking them, or intentionally misusing opioids, clinicians should consider urine drug testing to consider whether opioids can be discontinued abruptly or tapered, and clinicians should consider referral to substance use disorder (SUD) treatment.
- Urine drug testing is a tool that can be used to assist providers in assessing whether patients are using opioids as prescribed, using other substances or potentially diverting opioids.
- Clinicians should have an informed discussion with their patient about the serious risks associated with using these medications concurrently, included in recently released FDA boxed warnings.
- With Oregon's recent legalization of recreational use of marijuana, its use is relatively prevalent. Current data are limited on the interactions between opioids and marijuana. Clinicians and their organizations have an obligation to closely follow the emerging evidence on the use of marijuana for treatment of pain and adopt consistent best practice. Refer to the OHA medical marijuana prescribing guidelines, at https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/Physicians.aspx

Oregon Health Authority Acute Opioid Prescribing Guidelines

A task force of Oregon-based practitioners (similar to the OHA chronic opioid prescribing guidelines) created the OHA acute opioid prescribing guidelines.[45] The goal of these Oregon acute prescribing guidelines is to improve patient safety while emphasizing effective and compassionate treatment of acute pain.[45] These statewide guidelines are intended for patients who have had limited exposure to opioids in the past.[45] They are not intended for those who currently receive opioids nor for those with a history of substance use (or opioid use) disorder.[45] The guidelines are subdivided into eight sections to provide guidance on patient assessment, use of the PDMP, patient education, opioid selection and dosing, patient follow-up, and systemic responsibilities. In general, opioids should NOT be considered as first-line therapy for mild to moderate pain.[45] Mild to moderate pain can often be treated without opioids by recommending over-the-counter medications, and physical treatments such as ice and immobilization.[45] If non-opioid interventions are ineffective and opioids are appropriate, prescribe the lowest effective dose of short-acting opioids for less than 3 days; in cases of more severe acute pain, limit initial prescription to less than 7 day.[45]

Oregon Health Authority Opioid Tapering Guidelines

Beginning in March 2019, the OHA convened an expert panel to address guidelines for tapering opioids. This guidance should be publically available in late 2019.

After review, 1 guideline was excluded due to poor quality.[46]

New Formulations or Indications:

1. Apadaz™, a combination of benzhydrocodone and acetaminophen received FDA approval February 2018. Benzhydrocodone is a prodrug of the opioid agonist hydrocodone.[47] Immediate-release benzhydrocodone 6.12 mg is equivalent to 7.5 mg hydrocodone bitartrate.[47] Apadaz™ is indicated for 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.[47] Benzhydrocodone is a schedule II-controlled substance with a high potential for abuse similar to other opioids.[47] The manufacturer's label for Apadaz™ contains a black box warning about the risk of addiction, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, hepatotoxicity, cytochrome P450 3A4 drug interactions, and risks from concomitant use with benzodiazepines or other central nervous (CNS)

depressants.[47] The recommended dose for benzhydrocodone-acetaminophen is 1 or 2 tablets every 4 to 6 hours as needed for pain.[47] The safety of benzhydrocodone-acetaminophen was evaluated in a total of 200 healthy adults in 6 phase 1 studies.[47] The most common adverse events in these studies were nausea (21.5%), somnolence (18.5%), vomiting (13.0%), constipation (12.0%), pruritus (11.5%), dizziness (7.5%) and headache (6.0%).[47]

Theoretically, the potential benefits of benzhydrocodone/APAP are due to its prodrug approach where absorption is best achieved with oral administration as opposed to non-oral administration routes such as insufflation or injection.[48] One clinical trial of Apadaz™ focused on the abuse potential of intranasal benzhydrocodone administration.[49] Fifty-one subjects were randomized to receive 13.34 mg of intranasal benzhydrocodone and 15.0 mg of intranasal hydrocodone.[49] Blood samples were taken, and Drug Liking scores (assessed on a bipolar visual analog scale) were obtained throughout each dosing interval.[49] Total hydrocodone exposures were 20.3% and 19.5% lower, respectively, for benzhydrocodone compared with hydrocodone ($P < 0.0001$).[49] Drug Liking score, as assessed by maximal liking (Emax), was significantly lower for benzhydrocodone versus hydrocodone ($P = 0.004$), with 45% of subjects showing a 30% or greater reduction in Drug Liking Emax with benzhydrocodone.[49] Although benzhydrocodone has reduced bioavailability in non-oral routes of administration, it is still susceptible to oral abuse.[48]

2. Hydrocodone extended-release tablets (Vantrela™ ER) were FDA approved in January 2017. Extended release hydrocodone is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[50] Vantrela™ ER has a black box warning about the risk of addiction, life threatening respiratory depression, neonatal opioid withdrawal syndrome, cytochrome P450 3A4 drug interactions and risks from concomitant use with benzodiazepines or other CNS depressants.[50] For opioid-naïve and opioid non-tolerant patients, extended-release hydrocodone can be initiated with 15 mg tablets orally every 12 hours, and the dose increased every 3 to 7 days as needed, with a maximum recommended dose of 90 mg every 12 hours.[50] Higher doses have not been studied with regard to the effects of hydrocodone on the QT interval.[50] The safety of extended-release hydrocodone was evaluated in 1176 patients who were enrolled in two double-blind clinical trials and in two open-label studies.[50] Adverse reactions occurring in 2% or greater of patients in placebo-controlled trials included nausea, constipation, headache, somnolence, vomiting, dizziness, pruritus, fatigue, dry mouth, diarrhea, insomnia, and anxiety.[50] The safety and effectiveness of extended-release hydrocodone in patients less than 18 years of age has not been established.[50]

   Vantrela™ ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.[50] In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation.[50] Results support that Vantrela™ ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.[50] When Vantrela™ ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.[50]

3. A new oral formulation of sufentanil (Dsuvia®) was FDA-approved in November 2018. Oral sufentanil is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[51] The sublingual sufentanil tablet is supplied in a disposable, single-dose applicator and is only to be administered by the healthcare provider. Dsuvia® is not approved for home use, use in children, or duration of therapy greater than 72 hours. The manufacturer's label for Dsuvia® contains a black box warning about the risk of addiction, life-threatening respiratory depression, cytochrome P450 3A4 drug interactions, and risks from concomitant use with benzodiazepines or other CNS depressants associated with sufentanil administration.[51] The recommended dose of Dsuvia® is 30 mcg sublingually as needed with a minimum of 1 hour between doses, not to exceed 12 tablets (360 mcg) in 24 hours.[51]

The efficacy and safety of Dsuvia® were evaluated in a double-blind, multi-center, placebo-controlled RCT which enrolled 161 patients (age 18 to 69 years) with acute postoperative pain (pain intensity of ≥ 4 on a 0-10 NRS) after ambulatory abdominal surgery.[52] Patients were dosed with sufentanil 30 mcg or placebo as needed with a minimum of 60 minutes between doses. The primary efficacy endpoint was the time-weighted summed pain intensity difference over 12 hours (SPID12).[52] Patients using sufentanil had a statistically significantly higher SPID12 than patients using placebo (25.8 vs. 13.1, p< 0.001), with a difference of 12.7 [95% CI 7.16 to 18.23]) between groups.[52] Approximately 27% of patients in the sufentanil group and 65% of patients in the placebo group took rescue medication within the first 12 hours of the treatment phase (p<0.001).[52] The most frequently reported adverse events were nausea (26.7%) and headache (11.8%).[52]

4. Arymo™ ER (morphine sulfate extended-release) tablets received FDA approval in January 2017 for long-term opioid treatment and for which alternative treatment options are inadequate.[53] The manufacturer's label for Arymo™ ER contains a black box warning about the risk of addiction, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, and risks from concomitant use with benzodiazepines or other CNS depressants associated with morphine extended-release administration.[53] For opioid-naïve and opioid non-tolerant patients, the drug can be initiated with 15 mg tablets orally every 8 or 12 hour with a total daily dose not to exceed 120 mg.[53] In clinical trials, the most common adverse reactions with morphine sulfate extended-release formulations were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.[53]

   Arymo™ ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.[53] An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users; 38 subjects completed the study.[53] Treatment arms included manipulated Arymo™ ER 60 mg tablets (taken with juice), intact Arymo™ ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate extended-release tablets (mixed in juice), and placebo.[53] The study demonstrated that the oral administration of manipulated Arymo™ ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate extended-release tablets.[53] However, the difference between manipulated Arymo™ ER and crushed morphine sulfate extended-release tablets for Take Drug Again was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.[53] Abuse of Arymo™ ER by injection, as well as by the oral and nasal routes, is still possible.[53]

New FDA Safety Alerts: Recent safety alerts are presented in **Table 2.**

Table 2. Description of new FDA Safety Alerts[54]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tapentadol	Nucynta	December 2016	Warnings and Precautions	Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of tapentadol with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders

				and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range.
Tramadol and Codeine	Ultram	April 2017	Contraindications and Warnings	Restrict the use of codeine and tramadol medicines in children. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. Codeine and tramadol should not be used to treat pain after tonsillectomy or adenoidectomy in children younger than 18 years. Avoid use in adolescents between 12 to 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of breathing problems. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. The FDA also recommends against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.
Oxymorphone	Opana ER	June 2017	Removed from the U.S. market	Benefits no longer outweigh risks due to abuse associated with snorting or injecting.
Buprenorphine, Methadone	Subutex, Probuphine, Bunavail, Suboxone, Zubsolv, Dolophine, Methadose	September 2017	Safety Communication	FDA is advising that the opioid addiction medications should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks.
IR, ER, and LA Opioids		September 2018	Boxed Warning & Warnings and Precautions	New safety information regarding Opioid Analgesic REMS. Program includes training for providers regarding pain management, safe dispensing, and recommended monitoring. There is no mandatory federal requirement that prescribers take training and no precondition to prescribing or dispensing opioid analgesics to patients.
Prescription cough and cold medicines containing codeine or hydrocodone	Tuxarin ER, Tuzistra XR, Triacin C, FlowTuss, Obredon, Hycofenix, Rezira, Tussionex, Zutripro	January 2018	Boxed Warning	Limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. The FDA is also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.

Tramadol	Ultram	September 2018	Boxed Warning & Warnings and Precautions	Boxed warning added to label regarding risks of addiction, abuse, and misuse; Risk Evaluation and Mitigation strategy (REMS); life threatening respiratory depression; neonatal opioid withdrawal syndrome; interactions with drugs affecting cytochrome P450 isoenzymes; hepatotoxicity; and risks from concomitant use with benzodiazepines or other CNS depressants.
Opioid Pain Medications		April 2019	Safety Announcement	The U.S. Food and Drug Administration (FDA) has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances. The FDA is requiring changes to the prescribing label for these medicines that are intended for use in the outpatient setting. These changes are designed to promote safe tapering or discontinuing of opioids in patients who are physically dependent on the medication.

Abbreviations: ER = extended-release; IR = immediate-release; LA = long-acting; REMS = Risk Evaluation and Mitigation Strategy

Randomized Controlled Trials:

A total of 430 citations were manually reviewed from the initial literature search. After further review, 425 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 5 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Chang AK, et al.[55] DB, RCT	1.Ibuprofen 400 mg + APAP 1000 mg 2.Oxycodone 5 mg + APAP 325 mg 3.Hydrocodone 5 mg + APAP 300 mg 4.Codeine 30 mg + APAP 300mg 1 dose for each group	Patients aged 21-64 yo with moderate to severe acute extremity pain presenting to the ED Conducted at 2 urban EDs in NY N=411	Pain reduction at 2 hours as assessed by an 11 point NRS (0 = no pain, 10 = severe pain). MCID = 1.3 on the NRS	NRS pain score change from baseline at 2 hours 1. 4.3 (95% CI 3.6 to 4.9) 2. 4.4 (95% CI 3.7 to 5.0) 3. 3.5 (95% CI 2.9 to 4.2) 4. 3.9 (95% CI 3.2 to 4.5) No significant differences between groups at 2 hours (P=0.053) or 1 hour (P=0.13). None of the differences between analgesics met the MCID of 1.3 on the NRS pain score.

<table>
<tr>
<td>Krebs EE, et al.[56]

OL,RCT, Blinded outcome assessors</td>
<td>1.Opioid (IR morphine, oxycodone, or hydrocodone/APAP)
2.Nonopioid (APAP or NSAID)

Duration: 12 months</td>
<td>Patients with moderate to severe chronic back pain or hip or knee OA pain

N=240</td>
<td>Pain-related function over 12 months as assessed by BPI scale (range: 0-10; higher score = worse function or pain intensity)

MCID = 1 point improvement</td>
<td>BPI interference at 12 months
Opioid: 3.4
Non-opioid: 3.3
Difference = 0.1 (95% CI -0.5 to 0.7)

BPI severity at 12 months
Opioid: 4.0
Non-opioid: 3.5
Difference = 0.5 (95% CI 0.0 to 1.0)</td>
</tr>
<tr>
<td>Bedin A, et al.[57]

DB, PC, RCT</td>
<td>1.Duloxetine 60mg x 2 doses
2.Placebo x 2 doses

Duration: 48 hours</td>
<td>Patients aged 18 to 70 yo undergoing lumbar spinal fusion surgery

N=60</td>
<td>Total fentanyl consumption 48 hours after surgery</td>
<td>Fentanyl Consumption at 24 and 48 hours postoperatively (mcg)
<table>
<tr><th>Outcome</th><th>Duloxetine (n=28)</th><th>Placebo (n=29)</th><th>Mean Difference</th></tr>
<tr><td>Consumption (24 hours)</td><td>503 ± 19</td><td>726 ± 36</td><td>223 ± 39 (p<0.05)</td></tr>
<tr><td>Consumption (48 hours)</td><td>367 ± 19</td><td>546 ± 26</td><td>179 ± 33 (p<0.05)</td></tr>
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<tr>
<td>Best A, et al.[58]

DB, PC, RCT</td>
<td>1.Control: APAP 100mg + ibuprofen 400mg + Placebo
2.Intervention: APAP 1000mg + ibuprofen 400mg + codeine 60 mg

Duration: 48 hours</td>
<td>Adults requiring removal of 1 mandibular third molar and bone removal as an outpatient

N=131</td>
<td>Postoperative pain at 48 hours as measured by a 5 point verbal rating scale (1 = no pain; 5 = excruciating pain)</td>
<td>Global Pain Level During the First 48 Hours After Third Molar Surgery by Group
<table>
<tr><th>Pain Level</th><th>Control</th><th>Intervention</th><th>P Value</th></tr>
<tr><td>No Pain</td><td>9%</td><td>11%</td><td>0.52</td></tr>
<tr><td>Mild</td><td>45%</td><td>58%</td><td>NR</td></tr>
<tr><td>Moderate</td><td>37%</td><td>25%</td><td>NR</td></tr>
<tr><td>Excruciating</td><td>2%</td><td>2%</td><td>NR</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: APAP = acetaminophen; BPI = Brief Pain Inventory; CI = confidence interval; DB = double blind; ED = emergency department; IR = immediate-release; MCID = minimum clinically important difference; NR = not reported; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; NY = New York; OA = osteoarthritis; OL = open-label; PC = placebo controlled; RCT = randomized clinical trial; TID = three times a day; YO = years old

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Long-Acting Opioids

Generic	Brand	Form	Route	PDL
fentanyl	DURAGESIC	PATCH TD72	TRANSDERM	Y
fentanyl	FENTANYL	PATCH TD72	TRANSDERM	Y
morphine sulfate	MORPHINE SULFATE ER	TABLET ER	ORAL	Y
morphine sulfate	MS CONTIN	TABLET ER	ORAL	Y
buprenorphine	BUPRENORPHINE	PATCH TDWK	TRANSDERM	N
buprenorphine	BUTRANS	PATCH TDWK	TRANSDERM	N
buprenorphine HCl	BELBUCA	FILM	BUCCAL	N
fentanyl	FENTANYL	PATCH TD72	TRANSDERM	N
hydrocodone bitartrate	ZOHYDRO ER	CAP ER 12H	ORAL	N
hydrocodone bitartrate	HYSINGLA ER	TAB ER 24H	ORAL	N
hydromorphone HCl	EXALGO	TAB ER 24H	ORAL	N
hydromorphone HCl	HYDROMORPHONE ER	TAB ER 24H	ORAL	N
levorphanol tartrate	LEVORPHANOL TARTRATE	TABLET	ORAL	N
methadone HCl	METHADONE HCL	ORAL CONC	ORAL	N
methadone HCl	METHADONE INTENSOL	ORAL CONC	ORAL	N
methadone HCl	METHADOSE	ORAL CONC	ORAL	N
methadone HCl	METHADONE HCL	SOLUTION	ORAL	N
methadone HCl	DOLOPHINE HCL	TABLET	ORAL	N
methadone HCl	METHADONE HCL	TABLET	ORAL	N
methadone HCl	METHADONE HCL	TABLET SOL	ORAL	N
methadone HCl	METHADOSE	TABLET SOL	ORAL	N
morphine sulfate	KADIAN	CAP ER PEL	ORAL	N
morphine sulfate	MORPHINE SULFATE ER	CAP ER PEL	ORAL	N
morphine sulfate	MORPHINE SULFATE ER	CPMP 24HR	ORAL	N
morphine sulfate	MORPHABOND ER	TAB ER 12H	ORAL	N
morphine sulfate/naltrexone	EMBEDA	CAP ER PO	ORAL	N
oxycodone HCl	OXYCODONE HCL ER	TAB ER 12H	ORAL	N
oxycodone HCl	OXYCONTIN	TAB ER 12H	ORAL	N
oxycodone myristate	XTAMPZA ER	CAP SPR 12	ORAL	N
oxymorphone HCl	OPANA ER	TAB ER 12H	ORAL	N
oxymorphone HCl	OXYMORPHONE HCL ER	TAB ER 12H	ORAL	N
tapentadol HCl	NUCYNTA ER	TAB ER 12H	ORAL	N
tramadol HCl	CONZIP	CPBP 17-83	ORAL	N
tramadol HCl	TRAMADOL HCL ER	CPBP 17-83	ORAL	N
tramadol HCl	CONZIP	CPBP 25-75	ORAL	N

tramadol HCl	TRAMADOL HCL ER	CPBP 25-75	ORAL	N
tramadol HCl	TRAMADOL HCL ER	TAB ER 24H	ORAL	N
tramadol HCl	TRAMADOL HCL ER	TBMP 24HR	ORAL	N

Short-Acting Opioids

Generic	Brand	Form	Route	PDL
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ELIXIR	ORAL	Y
acetaminophen with codeine	CAPITAL W-CODEINE	ORAL SUSP	ORAL	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	SOLUTION	ORAL	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	TABLET	ORAL	Y
acetaminophen with codeine	TYLENOL-CODEINE NO.3	TABLET	ORAL	Y
acetaminophen with codeine	TYLENOL-CODEINE NO.4	TABLET	ORAL	Y
butorphanol tartrate	BUTORPHANOL TARTRATE	SPRAY	ORAL	Y
codeine sulfate	CODEINE SULFATE	TABLET	ORAL	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	SOLUTION	ORAL	Y
hydrocodone/acetaminophen	LORTAB	SOLUTION	ORAL	Y
hydrocodone/acetaminophen	HYDROCODONE/ACETAMINOPHEN	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET HD	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET PLUS	TABLET	ORAL	Y
hydrocodone/acetaminophen	NORCO	TABLET	ORAL	Y
hydromorphone HCl	HYDROMORPHONE HCL	SUPP.RECT	RECTAL	Y
hydromorphone HCl	DILAUDID	TABLET	ORAL	Y
hydromorphone HCl	HYDROMORPHONE HCL	TABLET	ORAL	Y
morphine sulfate	MORPHINE SULFATE	SOLUTION	ORAL	Y
morphine sulfate	MORPHINE SULFATE	SUPP.RECT	RECTAL	Y
morphine sulfate	MORPHINE SULFATE	TABLET	ORAL	Y
opium/belladonna alkaloids	BELLADONNA & OPIUM	SUPP.RECT	RECTAL	Y
opium/belladonna alkaloids	BELLADONNA-OPIUM	SUPP.RECT	RECTAL	Y
oxycodone HCl	OXYCODONE HCL	SOLUTION	ORAL	Y
oxycodone HCl	OXYCODONE HCL	TABLET	ORAL	Y
oxycodone HCl	ROXICODONE	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	CAPSULE	ORAL	Y
oxycodone HCl/acetaminophen	ENDOCET	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	NALOCET	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	PERCOCET	TABLET	ORAL	Y
tramadol HCl	TRAMADOL HCL	TABLET	ORAL	Y

tramadol HCl	ULTRAM	TABLET	ORAL	Y
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	CAPSULE	ORAL	N
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	TABLET	ORAL	N
acetaminophen/caff/dihydrocod	DVORAH	TABLET	ORAL	N
acetaminophen/caff/dihydrocod	PANLOR	TABLET	ORAL	N
butalbit/acetamin/caff/codeine	BUTALB-ACETAMINOPH-CAFF-CODEIN	CAPSULE	ORAL	N
butalbit/acetamin/caff/codeine	BUTALB-CAFF-ACETAMINOPH-CODEIN	CAPSULE	ORAL	N
butalbit/acetamin/caff/codeine	FIORICET WITH CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	ASA-BUTALB-CAFFEINE-CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	ASCOMP WITH CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	BUTALBITAL COMPOUND-CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	FIORINAL WITH CODEINE #3	CAPSULE	ORAL	N
fentanyl	SUBSYS	SPRAY	SUBLINGUAL	N
fentanyl citrate	ACTIQ	LOZENGE HD	BUCCAL	N
fentanyl citrate	FENTANYL CITRATE	LOZENGE HD	BUCCAL	N
fentanyl citrate	LAZANDA	SPRAY/PUMP	NASAL	N
fentanyl citrate	ABSTRAL	TAB SUBL	SUBLINGUAL	N
fentanyl citrate	FENTORA	TABLET EFF	BUCCAL	N
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ELIXIR	ORAL	N
hydrocodone/acetaminophen	ZAMICET	SOLUTION	ORAL	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	TABLET	ORAL	N
hydrocodone/acetaminophen	VERDROCET	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN ES	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN HP	TABLET	ORAL	N
hydrocodone/ibuprofen	HYDROCODONE-IBUPROFEN	TABLET	ORAL	N
hydrocodone/ibuprofen	IBUDONE	TABLET	ORAL	N
hydrocodone/ibuprofen	REPREXAIN	TABLET	ORAL	N
hydrocodone/ibuprofen	XYLON 10	TABLET	ORAL	N
hydromorphone HCl	DILAUDID	LIQUID	ORAL	N
hydromorphone HCl	HYDROMORPHONE HCL	LIQUID	ORAL	N
ibuprofen/oxycodone HCl	OXYCODONE HCL-IBUPROFEN	TABLET	ORAL	N
meperidine HCl	MEPERIDINE HCL	SOLUTION	ORAL	N
meperidine HCl	DEMEROL	TABLET	ORAL	N
meperidine HCl	MEPERIDINE HCL	TABLET	ORAL	N
morphine sulfate	MORPHINE SULFATE	SYRINGE	ORAL	N
morphine sulfate	ARYMO ER	TAB PO ER	ORAL	N
oxycodone HCl	OXYCODONE HCL	CAPSULE	ORAL	N
oxycodone HCl	OXYCODONE HCL	ORAL CONC	ORAL	N
oxycodone HCl	OXYCODONE HCL	SYRINGE	ORAL	N

oxycodone HCl	OXAYDO	TABLET ORL	ORAL	N
oxycodone HCl	ROXYBOND	TABLET ORL	ORAL	N
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	TABLET	ORAL	N
oxycodone HCl/acetaminophen	PRIMLEV	TABLET	ORAL	N
oxycodone HCl/acetaminophen	ROXICET	TABLET	ORAL	N
oxycodone HCl/aspirin	OXYCODONE HCL-ASPIRIN	TABLET	ORAL	N
oxymorphone HCl	NUMORPHAN	SUPP.RECT	RECTAL	N
oxymorphone HCl	OPANA	TABLET	ORAL	N
oxymorphone HCl	OXYMORPHONE HCL	TABLET	ORAL	N
pentazocine HCl/naloxone HCl	PENTAZOCINE-NALOXONE HCL	TABLET	ORAL	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE W/APAP	TABLET	ORAL	N
tapentadol HCl	NUCYNTA	TABLET	ORAL	N
tramadol HCl/acetaminophen	TRAMADOL HCL-ACETAMINOPHEN	TABLET	ORAL	N
tramadol HCl/acetaminophen	ULTRACET	TABLET	ORAL	N
aspirin/codeine phosphate	ASPIRIN W/CODEINE	TABLET	ORAL	

Appendix 2: Abstracts of Comparative Clinical Trials

1. Effect of a Single Dose of Oral Opioid and Non-opioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial[55]

Importance: The choice of analgesic to treat acute pain in the emergency department (ED) lacks a clear evidence base. The combination of ibuprofen and acetaminophen (paracetamol) may represent a viable non-opioid alternative.

Objectives: To compare the efficacy of 4 oral analgesics.

Design, Settings, and Participants: Randomized clinical trial conducted at 2 urban EDs in the Bronx, New York, which included 416 patients aged 21 to 64 years with moderate to severe acute extremity pain enrolled from July 2015 to August 2016.

Interventions: Participants (104 per each combination analgesic group) received 400 mg of ibuprofen and 1000 mg of acetaminophen; 5 mg of oxycodone and 325 mg of acetaminophen; 5 mg of hydrocodone and 300 mg of acetaminophen; or 30 mg of codeine and 300 mg of acetaminophen.

Main Outcomes and Measures: The primary outcome was the between-group difference in decline in pain 2 hours after ingestion. Pain intensity was assessed using an 11-point numerical rating scale (NRS), in which 0 indicates no pain and 10 indicates the worst possible pain. The predefined minimum clinically important difference was 1.3 on the NRS. Analysis of variance was used to test the overall between-group difference at P = .05 and 99.2% CIs adjusted for multiple pairwise comparisons.

Results: Of 416 patients randomized, 411 were analyzed (mean [SD] age, 37 [12] years; 199 [48%] women; 247 [60%] Latino). The baseline mean NRS pain score was 8.7 (SD, 1.3). At 2 hours, the mean NRS pain score decreased by 4.3 (95% CI, 3.6 to 4.9) in the ibuprofen and acetaminophen group; by 4.4 (95% CI, 3.7 to 5.0) in the oxycodone and acetaminophen group; by 3.5 (95% CI, 2.9 to 4.2) in the hydrocodone and acetaminophen group; and by 3.9 (95% CI, 3.2 to 4.5) in the codeine and acetaminophen group (P = .053). The largest difference in decline in the NRS pain score from baseline to 2 hours was between the oxycodone and acetaminophen group and the hydrocodone and acetaminophen group (0.9; 99.2% CI, -0.1 to 1.8), which was less than the minimum clinically important difference in NRS pain score of 1.3. Adverse events were not assessed.

Conclusions and Relevance: For patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at 2 hours among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics. Further research to assess adverse events and other dosing may be warranted.

2. Effect of Opioid vs Non-opioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain
The SPACE Randomized Clinical Trial[56]

Importance: Limited evidence is available regarding long-term outcomes of opioids compared with non-opioid medications for chronic pain.

Objective: To compare opioid vs non-opioid medications over 12 months on pain-related function, pain intensity, and adverse effects.

Design, Setting, and Participants: Pragmatic, 12-month, randomized trial with masked outcome assessment. Patients were recruited from Veterans Affairs primary care clinics from June 2013 through December 2015; follow-up was completed December 2016. Eligible patients had moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use. Of 265 patients enrolled, 25 withdrew prior to randomization and 240 were randomized.

Interventions: Both interventions (opioid and non-opioid medication therapy) followed a treat-to-target strategy aiming for improved pain and function. Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the non-opioid group, the first step was acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.

Main Outcomes and Measures: The primary outcome was pain-related function (Brief Pain Inventory [BPI] interference scale) over 12 months and the main secondary outcome was pain intensity (BPI severity scale). For both BPI scales (range, 0-10; higher scores = worse function or pain intensity), a 1-point improvement was clinically important. The primary adverse outcome was medication-related symptoms (patient-reported checklist; range, 0-19).

Results: Among 240 randomized patients (mean age, 58.3 years; women, 32 [13.0%]), 234 (97.5%) completed the trial. Groups did not significantly differ on pain-related function over 12 months (overall P = .58); mean 12-month BPI interference was 3.4 for the opioid group and 3.3 for the non-opioid group (difference, 0.1 [95% CI, -0.5 to 0.7]). Pain intensity was significantly better in the non-opioid group over 12 months (overall P = .03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the non-opioid group (difference, 0.5 [95% CI, 0.0 to 1.0]). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (overall P = .03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the non-opioid group (difference, 0.9 [95% CI, 0.3 to 1.5]).
Conclusions and Relevance: Treatment with opioids was not superior to treatment with non-opioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

3. Duloxetine as an Analgesic Reduces Opioid Consumption After Spine Surgery: A Randomized, Double-Blind, Controlled Study[57]
Objectives: Multimodal analgesia is widely advocated for the control of perioperative pain in an effort to reduce the use of opioid. Duloxetine is a selective inhibitor of serotonin and norepinephrine reuptake with efficacy for chronic pain conditions. The primary objective of this study was to evaluate the efficacy of two 60 mg oral doses of duloxetine in terms of fentanyl consumption during the postoperative period in patients undergoing elective spine surgery.
Materials and Methods: This study was prospective, double-blind, randomized, and placebo controlled. Patients received either 60 mg duloxetine or an identical placebo 1 hour before surgery and again the following morning. The study participants were allocated into 2 groups: Group C (control) participants received the placebo and Group D (duloxetine) participants received 60 mg duloxetine. The total consumption of fentanyl 48 hours after surgery was measured. Secondary end points were pain scores and the presence or absence of adverse effects, such as headache, nausea, vomiting, itching, dizziness, and drowsiness.
Results: Demographic characteristics did not differ between groups. There was a significant difference in fentanyl consumption in the first 24 hours between Groups C and D (mean difference, 223.11+/-39.32 [micro] g; P<0.001). Fentanyl consumption also differed between Groups C and D after 48 hours (mean difference, 179.35+/-32.55 [micro] g; P<0.000). The pain scores over 48 hours did not significantly differ between groups. The incidence of side-effects was similar in both groups.
Discussion: Duloxetine was effective as an adjunct for postoperative analgesia and reduced opioid consumption.

4. Efficacy of Codeine When Added to Paracetamol (Acetaminophen) and Ibuprofen for Relief of Postoperative Pain after Surgical Removal of Impacted Third Molars: A Double-Blinded Randomized Control Trial[58]
Purpose: The use of opioids in combination with non-opioids is common practice for acute pain management after third molar surgery. One such combination is paracetamol, ibuprofen, and codeine. The authors assessed the efficacy of codeine when added to a regimen of paracetamol and ibuprofen for pain relief after third molar surgery.
Materials and Methods: This study was a randomized, double-blinded, placebo-controlled trial conducted in patients undergoing the surgical removal of at least 1 impacted mandibular third molar requiring bone removal. Participants were randomly allocated to a control group (paracetamol 1,000 mg and ibuprofen 400 mg) or an intervention group (paracetamol 1,000 mg, ibuprofen 400 mg, and codeine 60 mg). All participants were treated under intravenous sedation and using identical surgical conditions and technique. Postoperative pain was assessed using the visual analog scale (VAS) every 3 hours (while awake) for the first 48 hours after surgery. Pain was globally assessed using a questionnaire on day 3 after surgery.
Results: There were 131 participants (36% men; control group, n = 67; intervention group, n = 64). Baseline characteristics were similar for the 2 groups. Data were analyzed using a modified intention-to-treat analysis and, for this, a linear mixed model was used. The model showed that the baseline VAS score was associated with subsequent VAS scores and that, with each 3-hour period, the VAS score increased by an average of 0.08. The treatment effect was not statistically meaningful, indicating there was no difference in recorded pain levels between the 2 groups during the first 48 hours after mandibular third molar surgery. Similarly, the 2 groups did not differ in their global ratings of postoperative pain.

Conclusion: Codeine 60 mg added to a regimen of paracetamol 1,000 mg and ibuprofen 400 mg does not improve analgesia after third molar surgery.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 4 2019 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 27, 2019

1. Buprenorphine/	3626
2. Codeine/	1627
3. Fentanyl/	7105
4. Hydromorphone/	724
5. Hydrocodone/	476
6. Meperidine/	1241
7. Morphine/ or Morphine Derivatives/	16800
8. Opium/	445
9. Oxycodone/	1792
10. Oxymorphone/	235
11. Tramadol/	2650
12. Levorphanol/	45
13. Methadone/	6308
14. Tapentadol/	277
15. Butorphanol/	648
16. Analgesics, Opioid/	35310
17. Pentazocine/	387
18. Propoxyphene.mp.	222
19. Tapentadol/	277
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	55465
21. Pain/ or Analgesics/ or Pain Management/	110961
22. 20 and 21	13063
23. limit 22 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	430

Appendix 4: Key Inclusion Criteria

Population	Patients with chronic pain
Intervention	Opioid Analgesics listed in **Appendix 1**
Comparator	Placebo or another opioid analgesic listed in **Appendix 1**
Outcomes	Reduced pain, improved functioning, adverse effects
Timing	Any study duration
Setting	Outpatient

Long-acting Opioid Analgesics

Goals:

- Restrict use of long-acting opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk vs. benefit.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

90 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain, or pain associated with sickle cell disease or severe burn injury are exempt from this PA.
- ~~This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.~~

Table 1. Daily Dose Threshold (90 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	

Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

Table 2. Specific Long-acting Opioid Products Subject to Quantity Limits per FDA-approved Labeling.

Drug Product	Quantity Limit	Drug Product	Quantity Limit	Drug Product	Quantity Limit
AVINZA	1 dose/day	HYSINGLA ER	2 doses/day	TROXYCA ER	2 doses/day
BELBUCA	2 doses/day	KADIAN	2 doses/day	XARTEMIS XR	4 doses/day
BUTRANS	1 patch/7 days	MORPHABOND	2 doses/day	XTAMPZA ER	2 doses/day
EMBEDA	2 doses/day	MS CONTIN	3 doses/day	ZOHYDRO ER	2 doses/day
EXALGO	1 dose/day	NUCYNTA ER	2 doses/day		
Fentanyl patch	1 dose/72 hr	OPANA ER	2 doses/day		
		OXYCONTIN	2 doses/day		

Approval Criteria	
1. What is the patient's diagnosis?	Record ICD10 code

2. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Go to # 11	**No:** Go to #12

11. Has the prescriber provided documentation of counseling the patient on the potential harms of concurrent use of opioids with a benzodiazepine or other central nervous system (CNS) depressant and determined that benefit outweighs risks?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #14 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
14. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Prioritized-List.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *9/19 (DM), 3/17 (MH); 11/16; 05/16*
Implementation: *Phase implementation initiated 8/21/17*

Short-acting Opioid Analgesics

Goals:

- Restrict use of short-acting opioid analgesics for acute conditions funded by the OHP.
- Promote use of preferred short-acting opioid analgesics.

Length of Authorization:

7 to 30 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Requires a PA:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 7 days in patients with new opioid starts or prescribed more frequently than 2 prescriptions every 90 days.~~.~~

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain or with pain associated with sickle cell disease or severe burn injury are exempt from this PA.
- ~~This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria~~.

Table 1. Daily Dose Threshold (90 morphine milligram equivalents per day (MME/day) of Oral Opioid Products.

Opioid	90 MME/day Dose	Notes

Benzhydrocodone	73.5 mg	
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.
Dihydrocodeine	360 mg	
Hydrocodone bitartrate	90 mg	
Hydromorphone	22.5 mg	
Levorphanol tartrate	8 mg	
Meperidine	900 mg	Meperidine is not recommended for management of chronic pain due to potential accumulation of toxic metabolites.
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	400 mg	400 mg/day is max dose and is not equivalent to 90 MME/day.

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Is the diagnosis funded by the OHP? Note: conditions such as fibromyalgia, TMJ, pelvic pain syndrome and tension headache are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. For patients with a history of chronic opioid use, short-term approval may be considered if a patient-specific taper plan is documented or for up to 30 days to allow providers time to develop a taper plan. Subsequent approvals must document progress toward the taper. Note: Management of opioid dependence is funded by the OHP.

3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for pain associated with sickle cell disease, severe burn injury or cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #6
6. Is the prescription for a product containing codeine or tramadol in a patient less than 19 years of age? Note: Cold symptoms are not funded on the prioritized list	**Yes:** Deny for medical appropriateness	**No:** Go to # 7
~~6.~~7. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #~~8~~7

~~7.~~8. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #~~9~~8
9. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Go to # 10	**No:** Go to #11
10. Has the prescriber provided documentation of counseling the patient on the potential harms of concurrent use of opioids with a benzodiazepine or other central nervous system (CNS) depressant and determined that benefit outweighs risks?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~11. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past 3 months the scheduled substances the patient has recently been prescribed from other providers?	**Yes:** Go to #~~10~~9	**No:** Pass to RPh. Deny; medical appropriateness.

~~9.~~12. Did the patient's pain originate from acute injury, flare, or surgery that occurred in the last 6 weeks?	**Yes:** Go to #13~~10~~	**No:** Go to #18~~75~~
~~10.~~13. Within this time period has a 5-day trial of ~~Has~~ at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried at its maximum effective dose and found to be ineffective or are contraindicated?	**Yes:** Go to #14~~1~~	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~14. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #15~~2~~	**No:** Approve for up to 30 days
~~12.~~15. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture?	**Yes:** Go to #16~~3~~	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~16. Is this the first opioid prescription the patient has received for this pain condition?	**Yes:** Approve for up to 7 days not to exceed 90 MME	**No:** Go to #17~~4~~
~~14.~~17. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Approve for up to 7 days not to exceed 90 MME	**No:** Pass to RPh. Deny; medical appropriateness.
~~15.~~18. Has the patient been prescribed opioid analgesics for more than 6 weeks ?	**Yes:** Go to #19~~6~~	**No:** Go to #11~~0~~

~~16.~~19. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.*	**Yes:** Document tool used to measure pain and/or function. Go to #2017~~17~~	**No:** Pass to RPh. May approve for up to 30 days one time. For future claims without documentation: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
~~17.~~20. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #2118~~18~~	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
~~18.~~21. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #2219~~19~~	**No:** Go to #230~~0~~
~~19.~~22. Have any of the following therapies also been prescribed and utilized by the patient: spinal manipulation, physical therapy, yoga or acupuncture?	**Yes:** Document additional therapy. Approve for up to 7 days not to exceed 90 MME. ~~Note:~~ ~~Risks outweigh benefits for back and spine conditions. OHP will not fund chronic use of opioids for back or spine conditions beginning 1/1/2018. Prescriber must develop a taper plan with the patient with a quit date before 1/1/2018. OHP funds treatment for patients who have become dependent or addicted to opioid analgesics.~~	**No:** Pass to RPh. Deny; medical appropriateness.

~~20.~~23. Does the total daily opioid dose exceed 90 MME (Table 1)?	**Yes:** Pass to RPh. May approve one time. For future claims: deny; medical appropriateness. For patients with a history of chronic opioid use, short-term approval may be considered if a patient-specific taper plan is documented or for up to 30 days to allow providers time to develop a taper plan. Subsequent approvals must document progress toward the taper. Note: Management of opioid dependence is funded by the OHP.	**No:** Approve for up to 30 days.

*The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738

Clinical Notes:

How to Discontinue Opioids.
Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

13. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
14. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
15. Establish the rate of taper based on safety considerations:
    a. Immediate discontinuation if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. Start with a taper of ≤10% of the original dose per week and assess the patient's functional and pain status at each visit.
16. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).

17. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
18. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
19. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
20. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
21. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
22. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
23. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.
24. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

Questions and answers about opioid coverage criteria effective August 21, 2017

Where can I find the new PA criteria for both short- and long-acting opioids?

On or after August 21, 2017, you can find the new PA criteria at www.orpdl.org/drugs under the "Analgesics" category.

Which opioids are restricted to 7 days or less for acute conditions?

Short-acting opioids such as hydrocodone/acetaminophen, oxycodone, and tramadol are restricted to 7 days or less for acute conditions. Long-acting opioids such as fentanyl and extended release morphine sulfate do not have this restriction.

You can find a comprehensive list of preferred and non-preferred short- and long-acting opioids on the Preferred Drug List (PDL) website.

- Short-acting: http://www.orpdl.org/drugs/drugclass.php?cid=1076.
- Long-acting: http://www.orpdl.org/drugs/drugclass.php?cid=1050.

Why are short-acting opioids restricted to 7 days or less for acute conditions?

This decision was based on the 2016 CDC guideline recommendations and will coincide with the Health Evidence Review Commission's 2014 coverage guidance.

What criteria apply to both short- and long-acting opioids?

Criteria for both short- and long-acting opioids require:

- A prescription that:
  - Is for a diagnosis which is funded by the OHP
  - Is not for pain associated with migraine or other type of headache, and
  - Does not exceed a total daily opioid dose of 90 morphine milligram equivalents (MME) per day.
- Documented verification that the patient:
  - Is not high-risk for opioid misuse or abuse,
  - Is not concurrently on other short- or long-acting opioids, and
  - Has sustained improvement of at least 30 percent in pain, function, or quality of life in the past 3 months (compared to baseline).

Do the new criteria apply to cancer-related pain or palliative care services?

No. Besides requiring an OHP-funded diagnosis, the additional new prior authorization criteria requirements do not apply if a patient is:

- Being treated for cancer-related pain (ICD-10 G89.3), or
- Under palliative care services (ICD-10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying.

Providing the ICD-10 diagnosis code on the prescription order and submitting it on the pharmacy claim may expedite the approval process.

Questions?

- **About pharmacy point of sale and prior authorizations for fee-for-service prescriptions:** Call the Oregon Pharmacy Call Center at 1-888-202-2126.
- **About physical health prescriptions for patients in a coordinated care organization (CCO):** Contact the CCO.

RETIRE THIS PA

Codeine

Goal(s):

Promote safe use of codeine in pediatric patients for analgesia or cough.

Length of Authorization:

- Up to 3 days

Requires PA:

All codeine products for patients under 19 years of age

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. What is the age of the patient?	**Ages 0-12 years:** Pass to RPh. Deny; medical appropriateness	**Ages 13-18 years:** Go to #3
3. Is the prescription for an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
4. Has the patient recently undergone tonsillectomy or adenoidectomy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Does the dose exceed 240 mg per day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve no more than 3-day supply

P&T Review: *5/16; 9/15; 7/15*
Implementation: *7/1/16; 8/25/15*

Drug Use Research & Management Program
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New Drug Evaluation: Tafamidis

Date of Review: September 2019
Generic Name: tafamidis

End Date of Literature Search: July 2019
Brand Name (Manufacturer): Vyndaqel® and Vyndamax™ (Pfizer Inc)

Research Questions:

1. Is tafamidis safe and effective in improving clinically meaningful outcomes, including improvements in mortality, cardiovascular related hospitalizations, disease progression, quality of life, and survival in patients with cardiomyopathy associated with transthyretin-mediated amyloidosis (ATTR)?
2. Are there subgroups of patients with ATTR cardiomyopathy for which tafamidis is more effective or associated with fewer adverse events?

Conclusions:

- There is low quality evidence based on one phase 3 randomized controlled trial that tafamidis meglumine 20 mg and 80 mg decrease the incidence of all-cause mortality (29.5% vs. 42.9%; HR 0.70; 95% CI 0.51-0.96) and cardiovascular (CV) related hospitalizations (52.3% vs. 60.5%; RR 0.68; 95% CI 0.56-0.81) when analyzed in a combined, hierarchical fashion ($p<0.001$) in patients with ATTR cardiomyopathy who have heart failure with a history of hospitalizations.
- There is insufficient evidence of no difference in efficacy or adverse events between tafamidis meglumine 20 mg and tafamidis 80 mg.
- There is low quality evidence of no difference in discontinuations due to adverse events and serious adverse events between tafamidis meglumine and placebo in patients with cardiomyopathy of ATTR.
- Subgroup analysis suggests a greater benefit in patients with less severe heart failure. There was no difference in all-cause mortality and CV-related hospitalizations were higher in those with heart failure New York Heart Association (NYHA) class III compared to placebo. Patients with NYHA class IV were excluded from the study. The precise time course to benefit and timing of initiation in the course of the disease remain unknown.

Recommendations:

- Maintain tafamidis as a non-preferred medication
- Modify prior authorization criteria for Drugs for Transthyretin-Mediated Amyloidosis to ensure appropriate use of tafamidis (**Appendix 2**).

Background:

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant disorder caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver that normally functions as a transporter of thyroxine and retinol (vitamin A).[1] The disorder presents in a spectrum of clinical presentations due to amyloid deposits, including a predominantly neurologic phenotype (familial amyloid polyneuropathy [FAP]) and a predominantly cardiac phenotype (familial cardiomyopathy [FAC]). However, hATTR can present with both cardiac and neurologic manifestations. There are over 120 TTR reported mutations, with at least 22 mutations associated with cardiomyopathy. Some mutations are more strongly associated with polyneuropathy (V30M) and some

with cardiomyopathy.[2] The most common mutation in the U.S. is the Val122I mutation, which typically leads to cardiomyopathy, with an estimated prevalence of 3.0% to 4.0% in the African American population.[3] The second most common mutation in the U.S. is T60A, which causes a mixed neuropathy and cardiomyopathy presentation.[3] Deterioration in activities of daily living and ambulation are seen due to neuropathic changes as well as autonomic dysfunction. Additionally, ATTR can affect multiple organ systems resulting in weight loss, wasting, difficulty walking, and alternating constipation and diarrhea, often due to autonomic nerve involvement. Cardiac manifestations due to deposition of amyloid fibrils in the myocardium can include heart failure, arrhythmias, orthostatic hypotension or sudden death due to severe conduction disorders. Cardiomyopathy can be associated with both hereditary and wild-type transthyretin amyloidosis (ATTRwt). Median survival for patients with hATTR cardiomyopathy is 2.5 years and median survival of ATTRwt is 3.6 years.[4]

Standard of care for ATTR has been limited to liver transplantation and administration of transthyretin tetramer stabilizers in addition to symptomatic management of heart failure.[5] Liver transplant has been the treatment of choice for those with neuropathy but no cardiac involvement. Current treatment for cardiomyopathy focuses on managing the symptoms, including diuretics and pacemaker placement although heart transplantation may be appropriate in some patients. Inotersen and patisiran were recently approved for hATTR-associated polyneuropathy. However, there have been no agents FDA approved in the United States for the cardiomyopathy phenotype. Tafamidis is a TTR stabilizer that binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation, the rate limiting step in amyloidogenesis. It is currently approved in Europe and several South American and Asian countries for early stage hATTR polyneuropathy. It was not approved in the U.S. in 2012 due to limited efficacy data. This is now the first Food and Drug Administration (FDA) approved drug for cardiomyopathy of ATTR and is available as two formulations (tafamidis meglumine and tafamidis free acid). Only the meglumine form was studied in phase 3 trials and the 2 formulations are not substitutable on a per mg basis.

The onset of symptoms of cardiomyopathy is usually greater than 60 years.[6] It is believed that this disease is widely underdiagnosed and may be the fourth most common cause of heart failure.[4] The goal of treatment in cardiomyopathy of ATTR is to prevent death from cardiac causes (heart failure, myocardial infarction, sudden cardiac death) and to decrease symptom burden (dyspnea, orthostatic hypotension, atrial fibrillation).

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Tafamidis was FDA-approved based on one phase 3 randomized controlled trial comparing pooled tafamidis meglumine (20 mg and 80 mg; n=264) to matching placebo (n=177) over 30 months in patients with heart failure due to confirmed (by biopsy) transthyretin amyloidosis.[7] The majority of patients had New York Heart Association (NYHA) Class II or III heart failure (67%), were male and had wild-type ATTR cardiomyopathy (75%). The primary outcome was all-cause mortality, followed by cardiovascular (CV) related hospitalizations, analyzed in a hierarchical fashion using the Finkelstein-Schoenfeld (FS) method. Comparisons were based on pooled tafamidis treatment groups versus placebo. Using the FS method, each subject is compared to every other subject within each stratum in a pair-wise manner for trial outcomes and ranked. Mortality carries a higher importance in ranking that does CV hospitalization. Thus, the pairwise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning a +1 to the “better” subject and a -1 to the “worse” subject.[4] This approach was used in response to the challenges posed by conducting clinical trials of rare diseases. However, it is difficult to interpret the results. The FS method combines both fatal and recurrent nonfatal events, but prioritizes fatal events, allowing for increased power.

Overall, the FS method demonstrated a statistically significant result for all-cause mortality followed by CV related hospitalizations when comparing pooled tafamidis to placebo (p<0.001), with a win ratio of 1.7 (95% CI 1.3 to 2.3).[7] The win ratio is the number of pairs of treated-patients "wins" divided by the number of placebo patient "wins". The FS is a test statistic, but not an easily interpretable summary of the results. Cox regression analyses also suggested a lower all-cause mortality with tafamidis compared to placebo (29.5% vs. 42.9%; HR 0.70; 95% CI 0.51-0.96).[7] This is based on the mean treatment effect of the study. The hazard ratio was not constant with respect to time, so it is difficult to calculate the number needed to treat per year. This effect was observed after approximately 18 months of therapy and was driven by CV death. Lastly, there was a significant reduction in patients with CV-related hospitalizations with tafamidis compared to placebo (52.3% vs. 60.5%; RR 0.68; 95% CI 0.56-0.81).[7]

Subgroup analysis suggests a larger effect size in those with less severe heart failure at baseline (NYHA class I or II). There was no significant difference in all-cause mortality in those with NYHA Class III and a worse effect from tafamidis compared to placebo for CV hospitalizations.[7]There was also a statistically significant improvement in quality of life, measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-QS) with an increase of 13.7 points from baseline compared to placebo.[7] A 5-point difference is thought to be clinically meaningful.[4]

There were unequal and high rates of overall attrition between pooled tafamidis (34%) and placebo (52%), increasing the risk of attrition bias. Attrition was mostly due to death and withdrawal by subject that was not further clarified. There did not appear to be a dose effect and the two doses had similar efficacy. However, the approved dose is 80 mg based on greater TTR tetramer stabilizer and no obvious different in toxicities seen in the phase 3 trial. TTR stabilization is not an acceptable surrogate endpoint to establish efficacy.[4] Additionally, approximately 80% of the study population was white. However, the prevalence of cardiomyopathy due to ATTR is approximately 3-4% in U.S. African Americans and is negligible in the Caucasian population.[6] Twenty four percent of randomized patients had the most common mutations (Val122Ile, Thr60Ala, and Ile68Leu). There are no data available on the use of tafamidis post-liver transplantation.

Tafamidis is approved as two formulations that are not equivalent per mg dose. Tafamidis meglumine (Vyndaqel®) 80 mg is approved based on the phase 3 trials. Tafamidis free acid (Vyndamax™) 61 mg was also approved based solely on bioequivalence/bioavailability studies to the 80 mg.[4]

Clinical Safety:

There were no significant differences in treatment emergent serious adverse events between tafamidis 20 mg (75%), 80 mg (75.6%) and placebo (79.1%). The most common serious adverse events were cardiac disorders, which reflect the underlying disease progression. There were also similar rates of discontinuations due to adverse events (**Table 2**). No adverse events were included in the drug labeling. Post-marketing studies will be done to evaluate for adverse events related to hypothyroidism and falls or balance disorders due to some initial safety signals. There was also a slight increase in infection-related adverse events with tafamidis 80 mg compared to placebo, with rates of pneumonia adverse events of 5.3, 6.3 and 8.0 per 100 patient years in placebo, 20 mg and 80 mg arms respectively.[4] However, there were no differences in serious adverse events related to pneumonia.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) All-cause mortality
2) Hospitalizations
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) All-cause mortality
2) Cardiovascular-related hospitalizations

Table 1. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Tafamidis is a selective stabilizer of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.
Oral Bioavailability	N/A
Distribution and Protein Binding	The apparent steady state volume of distribution of tafamidis is approximately 18.5 liters. Plasma protein binding of tafamidis is >99% in vitro.
Elimination	59% recovered unchanged in feces, 22% in urine as glucuronide metabolite
Half-Life	49 hours
Metabolism	Not fully characterized; glucuronidation has been observed

Abbreviations: N/A: not available; TTR: transthyretin

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.ATTR-ACT[7] Phase 3, MC, PD, PC, DB RCT	1. Pooled tafamidis group: a. Tafamidis 20 mg daily b. Tafamidis 80 mg daily 2. Placebo Over 30 months	Demographics: 74 y/o, 90% male, 80% white, 75% ATTRwt Key Inclusion Criteria: Heart failure, evidence of cardiac amyloid by ECHO and interventricular septal wall thickness > 12 nm, presence of amyloid deposits in biopsy tissue and TTR precursor protein identification, NT-proBNP ≥ 600 pg/ml, 6MWT > 100 meters Key Exclusion Criteria: NYHA class IV HF, light-chain amyloidosis, liver or heart transplantation, cardiac device, GFR < 25 ml/min, LFTs > 2 x ULN, mBMI < 600, concurrent treatment with NSAIDs, doxycycline, CCBs or digitalis, significant drug or alcohol abuse within last 5 years, HIV, HBV, HCV, males or females of childbearing potential unwilling	ITT: 1. 264 2. 177 PP: 1. 173 2. 85 Attrition: 1. 52 2. 54	Primary Outcome: All-cause death + CV hospitalization (FS method): Test statistic: 3.44 P value 0.0006 Secondary Outcomes: All-cause mortality 1. 78 (29.5%) 2. 76 (42.9%) HR 0.70; 95% CI 0.51 to 0.96 Patients with CV-related hospitalizations: 1. 107 (60.5%) 2. 138 (52.3%) RR 0.68; 95% CI 0.56-0.81 *p-values not provided	ARR 13.4%/ NNT 8 ARR 8.2%/ NNT 13	Discontinuations due to adverse events: 1.17 (6.4%) 2. 11 (6.2%) NS P Value and 95% CI NR	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; interactive response technology used for randomization and allocation concealment. Baseline characteristics similar between groups. Performance Bias: low; double-blinded; matching placebo Detection Bias: unclear blinding of outcome assessors Attrition Bias: high; mITT analysis done pooling both tafamidis dose groups. mITT includes all subjects who received at least one dose of medication and who had at least 1 post baseline efficacy evaluation. High and unequal attrition between tafamidis (34%) and placebo (52%). Reporting Bias: low; all outcomes reported Other Bias: unclear; funded by Pfizer. **Applicability**: Patient: significant exclusion criteria limits generalizability; mostly white (80%) males, while most common variant is present in 3 to 4% of blacks worldwide. 24% had the most common genetic mutations in the U.S. Intervention: 80 mg dose selected based on PK studies demonstrating maximal TTR stabilization with 80 mg. There did not appear to be a dose effect and the two doses had similar efficacy. TTR stabilization is not an acceptable surrogate endpoint to establish efficacy. Comparator: placebo appropriate; no other approved agents for comparison

		to use 2 methods of contraception, prior MI						Outcomes: Primary analysis used a hierarchical combination of all-cause mortality and frequency of all-cause hospitalization. Both tafamidis groups pooled and compared to placebo using the Finkelstein-Schoenfeld method Setting: multicenter; 60 sites in 13 countries (63% of patients enrolled at site in U.S).

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; ARR = absolute risk reduction; ATTR = transthyretin-mediated amyloidosis; ATTRwt = transthyretin-mediated amyloidosis wild type; CCB = calcium channel blocker; CI = confidence interval; CV = cardiovascular; DB = double blind; ECHO = echocardiogram; HIV: human immunodeficiency virus; FS = Finkelstein–Schoenfeld; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HF = heart failure ITT = intention to treat; LFT = liver function test; MC = multicenter; MI = myocardial infarction; mBMI = modified body mass index; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NSAID = nonsteroidal anti-inflammatory; NYHA = new York heart association; NR = not reported; PC = placebo controlled; PD = parallel-design; PK = pharmacokinetic; PP = per protocol; RCT = randomized controlled trial; RR: relative risk; TTR: transthyretin; ULN = upper limit of normal; U.S. = united states

References:

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4. FDA Center for Drug Evaluation and Research. Tafamidis Cilnical Review. Application Number: 211996Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211996Orig1s000,%20212161Orig1s000TOC.cfm.
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7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *The New England journal of medicine.* 2018;379(11):1007-1016.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYNDAQEL and VYNDAMAX safely and effectively. See full prescribing information for VYNDAQEL and VYNDAMAX.

VYNDAQEL® (tafamidis meglumine) capsules, for oral administration
Initial U.S. Approval: 2019

VYNDAMAX™ (tafamidis) capsules, for oral administration
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

VYNDAQEL and VYNDAMAX are transthyretin stabilizers indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is either:

- VYNDAQEL 80 mg orally once daily, or
- VYNDAMAX 61 mg orally once daily (2.1)
- VYNDAMAX and VYNDAQEL are not substitutable on a per mg basis. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: Tafamidis meglumine 20 mg and tafamidis 61 mg. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. (5)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2019

Drugs for Transthyretin-Mediated Amyloidosis (ATTR)

Goal(s):

- To limit utilization of medications for transthyretin mediated amyloidosis (ATTR) to FDA-approved indications and in populations with proven safety.

Length of Authorization:

Up to 6 months

Requires PA: (Both pharmacy and physician-administered claims)

- All medications indicated for ATTR

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: FDA approved therapies for ATTR amyloidosis

Drug	Indication
Inotersen	Polyneuropathy of hereditary ATTR
Patisiran	Polyneuropathy of hereditary ATTR
Tafamidis	Cardiomyopathy of ATTR (hereditary and wild type)

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
4. Is this an FDA approved indication of ATTR amyloidosis supported by transthyretin mutation proven by genetic testing (See Table 1)?	**Yes**: Go to #5 Document Genotype: _____	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have clinical signs and symptoms of disease (peripheral/autonomic neuropathy, motor disability, cardiovascular dysfunction)?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for or is the patient on concurrent use of more than one ATTR therapy (including diflunisal)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Has the patient had a liver transplantation?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for patisiran or inoteren?	**Yes:** Go to #9	**No:** Go to #16
9. Is baseline disease severity documented (polyneuropathy disability (PND) score and Familial amyloid polyneuropathy (FAP) stage)?	**Yes:** Document and Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Was the medication prescribed or in consultation with a neurologist?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the patient on Vitamin A supplementation or have a documented normal level?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
~~11.~~12. Is the request for patisiran?	**Yes**: Approve for 6 months	**No**: Go #13
~~12.~~13. Is the request for inotersen?	**Yes:** Go to # 14	**No:** Go to #16

Approval Criteria		
~~13.~~14. Has a baseline platelet count been obtained in the previous 3 months and are platelets ≥ 125 X 10^9/L?	**Yes:** Go to #15 Document baseline platelet count:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness.
~~14.~~15. Has baseline renal function been evaluated in the previous 3 months?	**Yes:** Approve for 6 months Document baseline serum creatinine and BUN:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the request for tafamidis?	**Yes:** Go to #17	**No:** Go to #19
17. Was the medication prescribed or in consultation with a cardiologist?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.
18. Does the patient have a medical history of heart failure (NYHA class I-III) with at least one prior hospitalization for heart failure?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
~~15.~~19. Is the request for a newly approved hATTR therapy and does the indication match the FDA approved indication?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient had a documented response to treatment including at least one of the following: a. Improved neurologic impairment b. Improved motor function c. Improved quality of life ~~c.~~d. Improved cardiac function	**Yes:** Go to #2	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
2. Is the prescribed medication tafamidis?	**Yes:** Approve for 12 months	**No:** Go to #3
~~2.~~3. Has the patient experienced stabilization OR improvement from baseline in one of the following: a. Baseline polyneuropathy disability (PND) score b. Familial amyloid polyneuropathy (FAP) stage	**Yes:** Go to #4	**No:** Pass to RPh; Deny (medical appropriateness)
~~3.~~4. Is the renewal for inotersen?	**Yes:** Go to #5	**No:** Approve for 12 months
~~4.~~5. Does the patient have a platelet count ≥ 100 X 10^9/L?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19; 7/19 (MH)
Implementation: TBD

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Class Update: Spinal Muscular Atrophy
New Drug Evaluation: **onasemnogene abeparvovec**, suspension for intravenous infusion

Date of Review: September 2019
Generic Name: onasemnogene abeparvovec-xioi

End Date of Literature Search: June 10, 2019
Brand Name (Manufacturer): Zolgensma® (AveXis, Inc.)
Dossier Received: yes

Research Questions:

1. Is there new published evidence regarding the safety and efficacy of nusinersen?
2. What is the comparative efficacy and effectiveness of onasemnogene abeparvovec in reducing symptoms and improving functional outcomes in patients with spinal muscular atrophy (SMA)?
3. What are the comparative harms of onasemnogene abeparvovec in SMA patients?
4. Are there certain sub-populations in which onasemnogene abeparvovec may be beneficial or cause more harm?
5. What is the evidence for the use of nusinersen after infusions of onasemnogene abeparvovec?

Conclusions:

Nusinersen

- The Canadian Agency for Drugs and Technologies in Health (CADTH) and United Kingdom (U.K.) National Institute for Health and Care Excellence (NICE) recently published evaluations of the available evidence for the use of nusinersen to treat SMA.[1,2]
- The CADTH clinical review evaluated 3 randomized clinical trials (RCTs), 4 phase 1 uncontrolled trials, and 2 phase 2 uncontrolled trials.[1] The observational and single-arm trials are of poor quality with high risk of bias due to open label study design, inadequate assessment of all patients included in the study, imbalanced baseline characteristics of randomized patients, and use of different nusinersen dosing regimens.[1] According to the clinical experts consulted for the CADTH review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number.[1] The shorter the duration since symptom onset, the younger the patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with nusinersen.[1]
- The NICE guidance concluded there is evidence to show nusinersen improves a range of clinical outcomes for people with early- (type 1) and later-onset (types 2 and 3) SMA.[2] Also, there is some evidence suggesting that nusinersen is effective for pre-symptomatic SMA.[2] However, there is insufficient long-term evidence, and the long-term benefits are highly uncertain.[2] Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.[2] This recommendation is narrower than the full marketing authorization in the U.K. or the United States because current evidence does not address use of nusinersen in patients with Type 0 or Type 4 SMA.[3,4]

Onasemnogene abeparvovec

- In August 2019 the Drug Effectiveness Review Project (DERP) completed a systematic review focused on clinical evidence for the use of onasemnogene abeparvovec in treating SMA.[5] One study evaluating effectiveness and harms of onasemnogene abeparvovec and 6 unpublished studies were identified. All studies were of poor quality due to trial design: i.e., uncontrolled interventional studies with indirect comparisons or historical controls.[5] No studies involved a head-to-head comparison of nusinersen with onasemnogene abeparvovec.[5] The published and unpublished literature includes samples of participants with SMA type 1 and 2 and pre-symptomatic SMA.[5] Based on indirect comparisons and assumed natural history of SMA, onasemnogene abeparvovec appears to improve survival, increase motor function and achievement of motor milestones in patients with SMA type 1.[5]
- The Food and Drug Administration (FDA) approval of onasemnogene abeparvovec was based on efficacy data from 1 ongoing phase 3 clinical trial (STR1VE) and a completed phase 1 clinical trial (START).[6,7] The FDA-approved indication for onasemnogene abeparvovec is for treatment of SMA patients with bi-allelic mutations in the SMN1 gene under the age of 2 years.[3]
- The START trial enrolled 15 patients with SMA Type 1; 3 patients in a low-dose cohort and 12 patients in a high-dose cohort.[7] In this Phase 1 trial, onasemnogene abeparvovec was administered as a single-dose intravenous infusion in an open-label, single-arm study design at high risk of bias. Poor quality data showed that by 24 months, 0 patients in the low-dose group achieved any of the normal motor milestones, and 1 became dependent on ventilatory support.[7] The high-dose group had better results at 24 months: 9 of the 12 patients (75%) were able to sit without support for at least 30 seconds, and 2 (17%) were able to crawl, pull to stand, and walk independently.[7] All patients in both cohorts were alive and at least 20 months of age after 24 months of the trial.[7]
- The ongoing phase 3 STR1VE trial has enrolled 21 patients (10 male and 11 female) with a mean age of 3.9 months (range 0.5 to 5.9 months) at the start of treatment.[6] All patients recruited for the study had genetically confirmed bi-allelic survival motor neuron (SMN) 1 gene deletions, two copies of the SMN2 gene, and experienced onset of clinical symptoms consistent with SMA before 6 months of age, which is characteristic of SMA Type 1. By the time of the interim data analysis, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation.[6] Ten of the 21 patients (47%) achieved the ability to sit without support for 30 seconds.[6] The data from this trial has not been published, and study quality could not be assessed.[6]
- The safety of onasemnogene abeparvovec was evaluated in 4 open-label studies (n=44) conducted in the United States. Twelve patients (29%) experienced elevated transaminases during the clinical trials with onasemnogene aberparvovec.[3] The onasemnogene abeparvovec manufacturer label contains a black box warning about the risk of acute serious liver injury and elevated aminotransferases which can occur after administration.[3] Patients with pre-existing liver impairment may be at higher risk for hepatic injury.[3] Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time).[3] All patients should receive systemic corticosteroids starting 1 day before onasemnogene abeparvovec infusion and continuing for at least 30 days after infusion.[3] Liver function should be monitored for at least 3 months after infusion.[3]
- Two patients who received onasemnogene abeparvovec died during the follow-up period. The study authors believed that one death was unrelated to treatment, and reported uncertainty about the cause of the other death.[5]
- There is insufficient evidence regarding long term safety and efficacy for the use onasemnogene abeparvovec in managing SMA. Most of the evidence was evaluated in SMA Type 1 patients. The FDA label indicates onasemnogene abeparvovec is approved for use in pediatric patients less than 2 years of age with SMA with biallelic mutations in the SMN1 gene, which is a broader indication than the current published evidence in children with SMA Type 1.
- No ongoing or planned head-to-head studies evaluating the effectiveness and harms of nusinersen after infusion of onasemnogene abeparvovec were identified.[5] The DERP authors interviewed representatives from AveXis and Biogen, the manufacturers of Zolgensma® and Spinraza®, respectively to assess the use of nusinersen after infusions of onasemnogene abeparvovec. Currently, there is insufficient evidence to support the subsequent use of nusinersen in patients who received an infusion of onasemnogene abeparvovec.[5]

Recommendations:

- Designate onasemnogene abeparvovec as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria to ensure one time administration of onasemnogene abeparvovec in appropriate SMA pediatric populations per the FDA labeling (**Appendix 4)**.
- Revise nusinersen PA criteria to include an assessment of onasemnogene abeparvovec administration prior to nusinersen initiation (**Appendix 4**).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

The first medication FDA-approved for all types of SMA in both pediatric and adult populations was nusinersen.[4] This drug was presented to the Pharmacy and Therapeutics (P and T) Committee at the July 2017 meeting. One unpublished, low quality phase 3 trial (ENDEAR) with high risk of bias demonstrated the efficacy of nusinersen in improving motor skills in infants who presented with SMA type 1 before the age of 7 months.[8] Response was defined as a participant who was alive and participating in the study and demonstrated at least a two-point (level) increase in the ability to kick or a one-point increase using the a Hammersmith Infant Neurological Exam (HINE)-2 assessment in head control, rolling, sitting, crawling, standing, or walking.[8] A greater percentage of subjects achieved HINE motor milestone response in the nusinersen group (40%) compared to the control group (0%) which was statistically significant ($p < 0.0001$).[8] Long term effects of nusinersen on survival and ventilator dependency are unknown at this time. Nusinersen can increase the risk of bleeding complications due to thrombocytopenia; platelet testing is required at baseline and before each dose.[4] Nusinersen also has a risk for renal toxicity. Quantitative spot urine testing is required at baseline and prior to each dose.[4] Additional trials in patients with SMA types 2 and 3 were ongoing and not published at the time of the 2017 P and T review. To ensure appropriate utilization of nusinersen in conditions with evidence of benefit, prior authorization (PA) criteria were implemented in 2017 (**Appendix 4**). In the past year, 8 patients within the Oregon Health Plan have had a diagnosis of SMA and a physician administered drug (PAD) claim for nusinersen administration. Seven of those patients were enrolled in a Coordinated Care Organization (CCO) and 1 patient was enrolled in Fee-For-Service (FFS). The Health Evidence Review Commission (HERC) has included SMA as a funded condition on lines 71, 292, 345, and 377.[9] In addition, SMA carrier screening for pregnant women is addressed in HERC Guideline Note D17.[9] Genetic screening for SMA (CPT 81239) is funded once in a lifetime.[9]

Background:

Spinal muscular atrophy is an autosomal recessive inherited neuromuscular disorder characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles and hypotonia. Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.[10] It is a rare disease and the incidence of SMA is estimated as 1 in 10,000 live births.[11] However, SMA is the most common genetic cause of death in infants due to respiratory insufficiency.[12] The phenotype is extremely variable, and patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[13] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. Infants with SMA Type 1 rarely achieve improvements in motor function or acquire motor developmental milestones.[12] The early signs of SMA Type 1 include generalized muscle weakness, hypotonia resulting in "floppiness," abnormal flexibility of the joints, absent tendon reflexes, twitching of the tongue, a frog-like position with the hips moved apart and knees bent or flexed, and an alert appearance.[14] Muscles of the face are not affected initially and mental development is usually normal.[14] Children with SMA type 2 exhibit muscle weakness that is more prominent in the lower extremities. They are able to sit unassisted, but are never able to independently walk. Respiratory failure is less severe and develops later in life compared to children with SMA type 1.[12] Children with SMA type 3 develop variable muscle weakness after 18 months of age and are able to walk, although as the disease progresses they may become wheelchair bound. Respiratory muscles are rarely affected and life expectancy is normal in this group of SMA patients.[12] SMA type 4 generally occurs in the second or third decade

of life and is the mildest form of the disease characterized by mild muscle weakness and normal life expectancy. The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[11]

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1% of cases
1 (severe)	1-3	Birth to 6 months	Never able to sit unassisted	<2 years	3.2 – 7.1 (45% of cases)
2 (intermediate)	2-3	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
3 (mild)	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5 – 4.6 (30 % of cases)
4 (adult)	≥ 4	Adult (2nd or 3rd decade)	Ambulatory	Normal	5% of cases

*Natural history may vary depending on supportive interventions

SMA is caused by biallelic deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13.[13] The SMN gene product, SMN protein, is essential for motor neuron development and function. The SMN gene region consists of a two almost identical genes: SMN1 and SMN2.[12] The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced, truncated, and nonfunctional SMN protein.[12] Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), only a small part (10–15%) of the mRNA transcripts contain exon 7, resulting in a small proportion of normal SMN protein (5-10%).[12] The number of copies of SMN2 correlate with the functional status of patients with SMA.[12] Infants with SMN1 biallelic deletions and only two copies of SMN2 have a 97% risk of SMA type 1.[7] The presence of 3 or more copies of SMN2 is associated with milder SMA symptoms. As the number of SMN2 copies correlates inversely with disease severity, moderate increases in SMN protein levels may have significant beneficial effects.[15]

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the United States.[16] Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction.[17] Other laboratory tests can include muscle enzyme creatine kinase, electrophysiological testing such as electromyography (EMG), and nerve conduction study with repetitive stimulation. These tests help to identify other muscle diseases, motor neuropathies, and disorders of neuromuscular junctions.[18] Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.[19] It is not possible to predict the severity of the SMA phenotype from carrier screening.

Due to the difficulties in quantifying motor abilities in these patients, several functional motor scales were developed to assess functional status in children with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients aged 4 months to 4 years.[20] The assessment incorporates the

limited abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16 item assessment of functional muscle strength and is scored on a 0 to 4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a total score ranging from 0 to 64 points. Higher scores on the CHOP-INTEND scale equate to better motor function. The maintenance of scores of more than 40 points has been considered to be clinically meaningful in SMA patients.[21] CHOP INTEND was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months).[22]

The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[23] It includes 3 sections with a total of 26 items assessing neurologic function, developmental milestone achievement, and behavioral assessment. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0 to 78). At 9 or 12 months, a score ≥ 73 is considered optimal.[23] Sequential use of the HINE allows the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[24] For example, in preterm infants assessed between six and 15 months corrected age, scores greater than 64 predict independent walking with a sensitivity of 98% and specificity of 85%.[24] Conversely, scores less than 52 are highly predictive of cerebral palsy and other severe motor impairments.[24] The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[17] Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 26.[25]

The Hammersmith Functional Motor Scale (HFMS) was developed by physical therapists to assess SMA type 2 and 3 patients.[26] The 20 item assessment provides information on motor ability and clinical progression in children with limited amubulation.[26] The HFMS motor assessment includes upper and lower limb activities as well as head and trunk control. Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4 point kneeling, crawling and standing. Each item is scored on a 3 point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter observer agreement > 99%.[26] Untreated patients with SMA Type II or Type III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.[26] For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running and jumping which resulted in the HFMS-Expanded (HFSME) score.[27]

There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Respiratory care includes the use of devices that improve ventilation, especially during sleep and viral illnesses when hypoventilation is most likely to occur, as well as methods to mechanically augment cough and clearance of respiratory secretions.[28] Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Full–time, noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition. Nutritional support includes the use of non-oral methods to deliver enteral nutrition, typically through a surgically placed feeding tube or temporary nasal tube, plus medical or surgical interventions to control gastroesophageal reflux.[28] Management of joint contractures and scoliosis involves aggressive physical therapy assessments, daily passive range of motion exercises, and use of bracing to facilitate and maintain optimal positioning of extremities and maintain the spine upright against gravity.[29]

Emerging therapies for SMA include modulation of SMN2 encoded full-length protein levels, SMN1 gene replacement, neuroprotection, and improvements of muscle strength and function.[10] In 2016, nusinersen was the first FDA-approved therapy for treatment of SMA. It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.[4]

Nusinersen is delivered by repeated intrathecal injections because ASOs do not efficiently cross the blood-brain barrier. The newest therapy, onasemnogene abeparvovec, formerly known as AVXS-101, is a SMN1 gene therapy that replaces the defective or missing SMN1 gene. Onasemnogene abeparvovec is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein, resulting in the normal development of motor neurons.[3] This therapy will be discussed in more depth later in this report. Novel oral therapies (risdiplam, branaplam) targeted towards improving survival in SMA patients are currently being evaluated in clinical trials.[30]

Systematic Reviews

Canadian Agency for Drugs and Technologies in Health: Nusinersen in Spinal Muscular Atrophy

In April 2019, CADTH published a clinical review of nusinersen treatment in SMA patients.[1] A total of 10 studies were included in the report.[1] Of the 10 studies, 3 were randomized controlled trials (ENDEAR, CHERISH, and EMBRACE), four were phase 1 uncontrolled trials along with their extension studies (CS1, CS2, CS10, and CS12), two were phase 2 uncontrolled trials (CS3A, and NURTURE), and 1 trial was an extension study that included participants from all trials except EMBRACE and NURTURE (and subsequent extension study SHINE).[1]

The five observational, non-comparative, case-series studies share a common limitation pertaining to the study design: the study design is descriptive in nature and cannot draw any association between an observed potential benefit and nusinersen treatment.[1] Without a control group, it is difficult to attribute any benefit observed to nusinersen alone, where other confounding factors are potentially present.[1] In addition, while objective clinical outcomes such as death or need for ventilation may have less potential to be biased by the open-label design of the study, other more subjective outcomes may be biased.[1] The NURTURE trial is an ongoing phase 2 study evaluating patients with pre-symptomatic SMA. The interim results from NURTURE may not reflect the final planned analysis of the predefined end point, especially as not all patients were assessed for all outcomes and this missing data might affect the results.[1] SHINE is also an ongoing extension study, and the interim results may be confounded by the drop-outs and missing data from the original trials.[1] The inclusion of patients who participated in dose-finding studies resulted in a heterogeneous population in terms of drug exposure, which also limits applicability to patients with SMA.[1] EMBRACE was a small exploratory phase II trial that showed significant imbalances in the baseline characteristics of randomized patients and was terminated prematurely.[1] CHERISH had a main limitation of using a nusinersen dosage schedule that is different from the Health Canada's recommended dosage schedule.[1] The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The FDA-approved nusinersen dosing interval is to initiate therapy with 4 loading doses followed by a maintenance dose once every 4 months after completion of the loading dose regimen.[4] The first 3 loading doses are administered at 14 day intervals followed by the fourth loading dose 30 days after the third dose.[4] The primary outcome, the change in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score from baseline to month 15, showed a statistically significant and potentially clinical meaningful difference between groups (least squares mean difference = 5.9 [95% confidence interval [CI], 3.7 to 8.1]).[1] A difference of 3 or more points was considered clinically meaningful.[1] This was further supported by a statistically significant difference in the first secondary outcome of HFMSE responders (≥ 3 points increase) at 15 months, showing a difference in proportion of 30.5% (95% CI, 12.74 to 48.31).[1] The second outcome to be tested in the statistical hierarchy (proportion of patients achieving new motor milestones at 15 months) failed to show statistical significance.[1] Overall, patients in the nusinersen group had a mean of 0.2 new motor milestones achieved (95% CI, 0.1 to 0.3) compared with a mean of –0.2 in the sham control group (95% CI,–0.4 to 0).[1]

According to the clinical experts consulted for the CADTH review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number.[1] Based on the available clinical data, the mechanism of action of nusinersen, and clinical experience, the two most important factors in determining an optimal response to treatment with nusinersen are time since symptom onset and the age of the patient; this is due to the fact that motor neuron deterioration is irreversible and early intervention is essential to prevent deterioration of motor function.[1] The shorter the duration since symptom onset, the younger the

patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with a drug such as nusinersen.[1] Clinical experts believe that an assessment of whether patients have responded to treatment should be carried out approximately 18 months after the initiation of the first dose of nusinersen, when patients are expected to have gained and maintained new motor milestones.[1] In adults with SMA (including those with type IV and type III who reach adulthood), it is unclear what the potential benefits of treatment with nusinersen would be, as clinical experience and natural history data indicate a plateau of the disease progression in the adult population.[1]

The December 2017 CADTH guidance recommends nusinersen use for the treatment of SMA if the following criteria are met:

- Under the care of a specialist with experience in the diagnosis and management of SMA.[31]
- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.[31]
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.[31]
- Disease duration less than 26 weeks with onset of clinical signs and symptoms consistent with SMA after the first week after birth and on or before 7 months of age.[31]
- Patient is not currently requiring permanent invasive ventilation.[31]
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
    - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2
    - or there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2);
    - or if permanent invasive ventilation is required.[31]

National Institute for Health and Care Excellence: Nusinersen in Spinal Muscular Atrophy

In July 2019, NICE published guidance for using nusinersen to treat SMA.[2] Clinical trial evidence shows that nusinersen improves a range of outcomes that are important to people with early- (type 1) and later-onset (types 2 and 3) SMA.[2] Also, there is some evidence suggesting that nusinersen is effective for pre-symptomatic SMA.[2] However, there is no long-term evidence, so the long-term benefits are highly uncertain.[2] The committee considered that further data collection would help address these uncertainties. Evidence from the clinical trials, including ENDEAR and CHERISH, is uncertain but relevant for decision making.[2]

Results from ENDEAR showed that, compared with sham, nusinersen statistically significantly improved event-free survival, overall survival and motor function in patients with type1 SMA.[2] The hazard ratio for event-free survival (defined as time to death or permanent ventilation) was 0.53 (95% confidence interval [CI] 0.32 to 0.89; p=0.005).[2] The hazard ratio for overall survival was 0.37 (95% CI 0.18 to 0.77; p=0.004).[2] In terms of motor function, 51% of patients in the nusinersen group reached motor milestone responses compared with none in the control group (as measured by a modified version of the HINE-2).[2]

Results from CHERISH showed that, compared with sham, nusinersen statistically significantly improved motor function of children with later-onset SMA.[2] Motor function as measured by HFMSE had a least-squares mean difference of 4.9 (95% CI 3.1 to 6.7; p<0.001).[2] The NICE committee agreed that nusinersen provides important health benefits for people with later-onset SMA, but it was unclear how this affects survival because there were no deaths during the CHERISH trial.[2] The committee noted that both ENDEAR and CHERISH had short follow-up periods: ENDEAR had a follow-up of only 13 months, 16% of people having nusinersen and 39% of those having sham died; CHERISH had a follow-up of only 15 months, and there were no deaths.[2] However, it is possible that some people with SMA may not reach motor function milestones despite having nusinersen, and it is unclear what the relationship is between improvements in motor function and a long term survival benefit.[2] Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.[2] This

recommendation is narrower than the full marketing authorization in the U.K. or the United States because current evidence does not address use of nusinersen in Type 0 or Type 4 SMA.[2,4]

The NICE Managed Care Access agreement entry criteria include:[32]

- No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline
- Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated
- Must not be type IV SMA patient i.e. must not have symptom onset at or after 19 years of age
- Must not be type 0 SMA patient

Drug Effectiveness Review Project 2019: Clinical Evidence Use of Onasemnogene Abeparvovec in Treating Spinal Muscular Atrophy

In August 2019, the Drug Effectiveness Review Project (DERP) completed a systematic review focused on clinical evidence for the use of onasemnogene abeparvovec in treating SMA.[5] The literature search was conducted through June 2019. In addition, DERP authors interviewed representatives from AveXis and Biogen, the manufacturers of Zolgensma® and Spinraza®, respectively. One published study that reported on effectiveness and harms of onasemnogene abeparvovec and 6 unpublished studies were identified. All studies were uncontrolled interventional studies or had indirect comparisons.[5] No studies involved a head-to-head comparison of nusinersen with onasemnogene abeparvovec. The published and unpublished literature includes samples of participants with SMA type 1 and 2 and pre-symptomatic SMA.[5] Six ongoing studies with expected completion dates ranging from November 2019 to December 2033 were also identified.[5] Five of the 6 ongoing studies have preliminary data.[5] The largest estimated sample consists of 33 participants.[5] SMA type 1 is being studied in 4 ongoing studies and SMA type 2 and pre-symptomatic SMA are being evaluated in 1 study each.[5] One ongoing study (STRONG) is evaluating the intrathecal administration of onasemnogene abeparvovec; all others (including the published evidence) are evaluating IV administration of onasemnogene abeparvovec.[5] No ongoing or planned head-to-head studies were identified which evaluate the effectiveness and harms of nusinersen after infusion of onasemnogene abeparvovec.[5]

The START trial (NCT 02122952) enrolled patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and two copies of SMN2.[7] This study was rated as poor quality because it lacked a control group or a direct control group (i.e., concurrently selected in the same source population), precluding determination with confidence that the intervention was causing the outcome.[5] Furthermore, the investigators and outcome assessors were unblinded to treatment allocation.[5] Unblinding of outcome assessors increases risk of bias particularly for subjective outcomes, such as the CHOP-INTEND, because knowledge of treatment assignment may influence their outcome evaluation.[5] The sample size of the study was also very small (15 participants) and industry was involved in funding and conducting the study, which has been shown to introduce bias.[5] However, an independent data and safety monitoring board (DSMB) was used.[5] An independent DSMB generally provides oversight of study data and an objective determination of adverse events and serious harms.[5]

Two years after infusion of onasemnogene abeparvovec, all participants in the high-dose group (n = 12) were alive and none required permanent ventilation.[7] However, about half of the sample required noninvasive ventilation.[7] Nearly all participants (11 of 12; 92%) achieved motor milestones; the following were potentially the most clinically important: 2 of 12 participants (17%) achieved the ability to stand with assistance and 2 of 12 (17%) achieved the ability to walk independently.[7] At baseline, average CHOP-INTEND scores were 16.3 (low-dose group) and 28.2 (high-dose group).[7] The maximum score of CHOP-INTEND is 64. In the high-dose group, CHOP-INTEND scores, on average, improved by 9.8 and 15.4 points from baseline to 1 and 3 months, respectively.[5] By the study cutoff, average increases in CHOP-INTEND scores were 7.7 in the low-dose group and 24.6 points in the high-dose group.[5]

The only adverse event that the authors believed to be treatment-related was elevated serum aminotransferase levels (4 of 12; 33%), which was managed with prednisolone.[5] One patient had up to 35 times the upper limit of the normal range for alanine aminotransferase (ALT) and 37 times the upper limit of the normal range for aspartate aminotransferase (AST).[5] Elevated serum aminotransferase levels resolved with prednisolone treatment.[5]

Key DERP conclusions include:

- Based on indirect comparisons and assumed natural history of SMA, onasemnogene abeparvovec appears to improve survival, increase motor function and achievement of motor milestones in patients with SMA type 1.[5]
- Unpublished studies of pre-symptomatic SMA showed improvements in motor function and achievement of motor milestones; however, the validity of these findings is uncertain because no control group was used. The 1 unpublished study of SMA type 2, which tested intrathecally administered onasemnogene abeparvovec, also showed improvements in achievement of motor milestones and a slight reduction in liver-related adverse events relative to studies of intravenous (IV) administration of onasemnogene abeparvovec.[5]
- The main harm related to treatment with onasemnogene abeparvovec was elevated serum aminotransferase levels, potentially indicating liver or muscle injury.[5] This issue was resolved with use of corticosteroids. Two patients who received onasemnogene abeparvovec died during the follow-up period. The study authors believed that one death was unrelated to treatment, and reported uncertainty about the cause of the other death.[5]
- Concerns about this limited body of evidence include the small number of individuals studied, uncontrolled study designs, uncertain long-term benefits and harms, and the long-term durability of onasemnogene abeparvovec because it does not self-replicate.[5]
- AveXis representatives stated that there is not a biologically plausible reason to use nusinersen after infusion of onasemnogene abeparvovec.[5] Biogen representatives noted that use of nusinersen after infusion of onasemnogene abeparvovec has not been studied and have stated that using nusinersen after onasemnogene abeparvovec should be a decision between a patient and provider.[5] AveXis and Biogen have no current plans to study the effectiveness and harms of using nusinersen after infusion of onasemnogene abeparvovec.[5]

Randomized Controlled Trials

A total of 74 citations were manually reviewed from the initial literature search. After further review, 73 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in **Table 2** below. The full abstract is included in **Appendix 3.**

Table 2. Summary of Pivotal Study for Nusinersen

Study	Comparison	Population	Primary Outcome	Results
Mercuri et al.[33] CHERISH Phase 3 DB, PC, MC, RCT N=126	1. 12 mg nusinersen administered intrathecal by lumbar puncture days 1, 29, 85, and 274 2. Sham procedure on days 1, 29, 85, and 274 Over 9 months with 6 month follow up	-Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote -Onset of clinical signs and symptoms consistent with SMA at < 6 months of age -Males and females 2 to 12 years of age -Could sit independently, but has never had the ability to walk independently ---Motor Function Score (HFMSE) ≥ 10 and ≤ 54 at screening	Change from baseline in HFMSE score at 15 months	Change in HFSME score from baseline to month 15 1. +4 2. -1.9 LSMD = 5.9; 95% CI 3.7 to 8.1 P<0.001 *Favors nusinersen over sham procedure*

Abbreviations: HFSME = Hammersmith Functional Motor Scale; LSMD = least squares mean difference; MC = multicenter; PC = placebo controlled; RCT = randomized control trial; SMA = spinal muscular atrophy

New Drug Evaluation: Onasemnogene abeparvovec (Zolgensma®)
See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Onasemnogene abeparvovec (Zolgensma®) is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[3] The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity.[6] Onasemnogene abeparvovec therapy is designed to deliver a copy of the SMN gene to motor neurons, which restores the ability of these cells to produce SMN protein. The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.[3] Onasemnogene abeparvovec was granted breakthrough therapy designation after the FDA fast-tracked a priority review of this treatment.[6] Onasemnogene abeparvovec also received orphan drug designation, which provides incentives to encourage the development of drugs for rare diseases.[6] The FDA also awarded the manufacturer a rare pediatric disease priority review voucher, under a program intended to encourage the development of new drugs and biological products for the prevention and treatment of certain rare pediatric diseases.[6] The product is shipped frozen and supplied as a customized kit to meet individualized weight based dosing requirements for each patient.

Clinical Efficacy:
The FDA approval of onasemnogene abeparvovec was based on data from an ongoing Phase 3 clinical trial (STR1VE) and a completed Phase 1 clinical trial (START).[6,7] Efficacy was established based on survival, and achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the CHOP-INTEND scale.

The START trial (NCT 02122952) enrolled patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and two copies of SMN2. Patients with a c.859G→C exon 7 mutation of SMN2 were excluded from the trial as this mutation is believed to be associated with a milder clinical phenotype.[7] Three patients were enrolled in a low-dose cohort and 12 patients in a high-dose cohort.[7] Onasemnogene abeparvovec was administered as a single-dose intravenous infusion in an open-label, single-arm study design. At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months and 3.4 months in the high-dose cohort.[7] At baseline, average CHOP-INTEND scores were 16.3 (low-dose group) and 28.2 (high-dose group).[7] The dosage received by patients in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. Follow-up was conducted on days 7, 14, 21, and 30 followed by monthly visits through 12 months post-dosing, and then every three months through two years post-dosing. The primary endpoint was safety and the secondary endpoints were efficacy based on duration of survival and achievement of normal motor milestones. Due to serum aminotransferase elevations in 1 patient in the low dose cohort, the protocol was amended so that all subsequent patients started oral prednisolone 1 mg/kg/day, 24 hours before the administration of onasemnogene abeparvovec, and continued oral corticosteroids for 30 days.[7] No patients in the low-dose group achieved any of the normal motor milestones, and 1 became dependent on ventilatory support at after 24 months of follow-up.[7] The high-dose group had

better results at 24 months: 9 of the 12 patients (75%) were able to sit without support for at least 30 seconds, and 2 (17%) were able to crawl, pull to stand, and walk independently.[7] By the study cutoff, average increases in CHOP-INTEND scores were 7.7 in the low-dose group and 24.6 points in the high-dose group.[7] All patients in both cohorts were alive and at least 20 months of age after 24 months of the trial.[7] The precise dosages of onasemnogene abeparvovec received by patients in the START trial are unclear due to a change in the method of measuring onasemnogene abeparvovec concentration and decreases in the concentration of stored onasemnogene abeparvovec over time.[6] In subsequent trials, the onasemnogene abeparvovec dose was directly measured by a validated and more precise droplet digital polymerase chain reaction method.[6]

The START trial was a poor quality trial due to its small sample size, single arm, open-label study design and significant differences in baseline characteristics between the low dose and high dose cohorts. Investigators were not blinded to treatment, which increased the risk of bias when completing motor function assessments such as the CHOP-INTEND instrument. More details about the Phase 1 START trial are presented in **Table 5.**

STR1VE, an ongoing, open-label, single-arm phase 3 study (NCT 03505099), is currently evaluating patients with infantile-onset SMA using available natural history data as a control.[6] The data from this trial has not been published, so details about this trial were obtained from the FDA approval summary report.[6] All patients recruited for the study had genetically confirmed bi-allelic SMN1 gene deletions, two copies of the SMN2 gene, and experienced onset of clinical symptoms consistent with SMA before 6 months of age.[6] Based on historical categorization of SMA, many of the patients enrolled would have SMA type 1. As in the START trial, onasemnogene abeparvovec was delivered as a single-dose intravenous infusion; however the dose was increased to 1.1×10^{14} vg per kg for all subjects based on poor results from the low dose cohort in the START trial.[6] Sixteen sites in the United States are participating in this trial. STRIVE has enrolled 21 patients (10 male and 11 female) with a mean age of 3.9 months (range 0.5 to 5.9 months) at the start of treatment.[6] The mean CHOP-INTEND score at baseline was 31.0 (range 18 to 47).[6] The 2 primary efficacy endpoints are survival at 14 months of age and the proportion of patients achieving the milestone of sitting without support for least 30 seconds at 18 months of age.[6] Survival was defined as previously described. By the time of data cutoff, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation.[6] Ten of the 21 patients (47%) achieved the ability to sit without support for 30 seconds.[6] Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive beyond 14 months of age.[6]

SPR1NT is another ongoing Phase 3 trial currently being conducted in the U.S., Canada, Europe, Australia and Asia in the treatment of patients with pre-symptomatic SMA possessing 2 or 3 copies of SMN2. As of March 2019, 18 patients had been enrolled and treated in this study. An additional phase 1 trial (STRONG) is evaluating 3 different doses of intrathecal injection of onasemnogene abeparvovec as preliminary results indicate less liver toxicity with this route of administration.[5]

Clinical Safety:

Adverse effects associated with the use of onasemnogene abeparvovec during clinical trials included elevated aminotransferases and vomiting.[3] The incidence of adverse effects that occurred more frequently than 5% are outlined in **Table 3**. Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, and increases in cardiac troponin-I levels were observed at different time points after onasemnogene abeparvovec infusion.[6] The clinical importance of these findings is not known as there were no clinical cardiac sequelae.[6]

Table 3. Adverse Reactions Following Treatment with Onasemnogene Abeparvovec (n=44)[3]

Adverse Reactions	Number of Patients (%)
Elevated aminotransferase	12 (27.3%)
Vomiting	3 (6.8%)

The onasemnogene abeparvovec manufacturer label contains a boxed warning about the risk of acute serious liver injury and elevated aminotransferases which can occur after infusion.[3] Patients with pre-existing liver impairment may be at higher risk for hepatic injury. Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time).[3] All patients should receive systemic corticosteroids starting 1 day before onasemnogene abeparvovec infusion and continuing up to 60 days after infusion.[3] Liver function should be monitored for at least 3 months after infusion.[3]

In the onasemnogene abeparvovec clinical trials, patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an enzyme-linked immunosorbent assay (ELISA).[6] The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.[6] Following onasemnogene abeparvovec infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. In the completed Phase 1 clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients.[6] High anti-AAV9 antibody titers resulting from the initial onasemnogene abeparvovec infusion are expected to preclude the possibility of re-administration of AAV9 vector-based gene therapy.[6]

Currently, there is insufficient data to establish safety and insufficient evidence for efficacy, although observational data is encouraging. The manufacturer of onasemnogene abeparvovec plans to conduct long-term follow up studies to collect safety and efficacy information on patients who participate in clinical trials for this gene therapy. Safety monitoring with be conducted for 15 years with in-person yearly visits for the first 5 years followed by yearly telephonic contact for 10 years.[6]

Look-alike / Sound-alike Error Risk Potential: No issues identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Survival
2) Respiratory support (need for ventilation)
3) Functional improvement (independently sit, stand or walk)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Survival at 14 months of age
2) Ability to sit unsupported ≥ 30 seconds by 18 months of age

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Gene replacement therapy
Oral Bioavailability	N/A: administered via intravenous infusion
Distribution and Protein Binding	Highest vector DNA levels detected in the liver

Elimination	Vector DNA detected in saliva, urine and stool after infusion
Half-Life	N/A
Metabolism	N/A

Abbreviations: DNA = deoxyribonucleic acid; N/A = not applicable

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mendell[7] START trial NCT02122952 Phase 1, OL N=15	1. Low dose: onasemnogene abeparvovec 6.7×10^{13} vg per kg x 1 IV infusion 2. High dose: onasemnogene abeparvovec 2.0×10^{14} vg per kg x 1 IV infusion 2 year study with long-term safety follow-up	Demographics: 1. Mean age Low dose: 6.3 months High dose: 3.4 months 2. Mean weight: 5.7 to 6.6 kg 3.Gender: female 58% 3. Race: White: 92% 4. Baseline CHOP-INTEND scores- Low dose: 16.3 High dose:28.2 Key Inclusion Criteria: 1. Genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and 2 copies of SMN2 2. Onset of disease from birth to 6 months 3. Hypotonia assessed by TIMP and 2 SD below the mean Key Exclusion Criteria: 1. Active viral infection 2. Use of ventilator support 3. Anti-AAV9 antibody titer >1:50 4. Patients with c.859G→C disease modifier in exon 7 of SMN2	ITT: 1. 3 2. 12 PP: 1. 3 2. 12 Attrition: 1. 0 2. 0	Primary Endpoint: 1.Safety: Number of patients who developed unacceptable toxicity (i.e.; 1 Grade 3 or 2 Grade 2 treatment-related toxicities) 1. 1 (33%) 2. 3 (25%) Secondary Endpoints: 1.Survival at 24 months 1. 3 (100%) 2. 12 (100%) 2. Sitting without support for ≥ 30 seconds 1. 0 (0%) 2. 9 (75%) 3.Need for permanent ventilator assistance (16 hours per day) at 20 months of age 1. 1 (33%) 2. 0 (0%) 3.Mean increase in CHOP INTEND score from baseline at 25 months 1. 7.7 points 2. 24.6 points p-value and CI NR	NA	Any AE 1. 3 (100%) 2. 12 (100%) Serious AE 1. 3 (100%) 2. 10 (83%) Treatment associated-AE 1. 1 (33%) 2. 3 (25%) p-value and CI NR for all	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Trial was not randomized. Performance Bias: High. Investigators not blinded to treatment. Detection Bias: High. Open label, single arm trial design. Attrition Bias: Low. No patients withdrew from trial and at 24 month follow-up all patients were alive. Reporting Bias: Low. Trial protocol available in supplementary materials. Other Bias: Unclear. Sponsored by the manufacturer AveXis, who provided data management and statistical analysis. Several authors received financial support from AveXis either through grants or personal fees. **Applicability**: Patient: Patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and 2 copies of SMN2. Not clear if this was limited to SMA type 1 patients. Intervention: Dose finding and safety assessment in a phase 1 trial. Comparator: Historical controls Outcomes: Safety is the primary endpoint. Secondary endpoints included survival and motor achievements. Setting: Single site: Nationwide Children's Hospital in Columbus, Ohio

Abbreviations : AE = adverse event; ARR = absolute risk reduction; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; ITT = intention to treat; IV = intravenous; kg = kilogram; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; SD = standard deviations; SMA = spinal muscular atrophy; SMN = survival motor neuron; TIMP = Test for Infant Motor Performance; vg = vector genomes

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZOLGENSMA safely and effectively. See full prescribing information for ZOLGENSMA.

ZOLGENSMA® (onasemnogene abeparvovec-xioi)
Suspension for intravenous infusion
Initial U.S. Approval: 2019

WARNING: ACUTE SERIOUS LIVER INJURY
See full prescribing information for complete boxed warning.
- **Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. (5.1)**
- **Patients with pre-existing liver impairment may be at higher risk. (8.6)**
- **Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion (2.1) (2.3).**

INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene. (1)
Limitation of Use:
- The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated. (1, 6.2)
- The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated. (1, 14)

DOSAGE AND ADMINISTRATION

ZOLGENSMA is for single-dose intravenous infusion only (2).
- The recommended dosage of ZOLGENSMA is 1.1×10^{14} vector genomes (vg) per kg of body weight.
- Administer ZOLGENSMA as an intravenous infusion over 60 minutes. (2.1, 2.3)
- Starting one day prior to ZOLGENSMA infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30-day period of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose over the next 28 days. Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone. (2.1)

DOSAGE FORMS AND STRENGTHS

ZOLGENSMA is a suspension for intravenous infusion, supplied as single-use vials.
ZOLGENSMA is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL Each vial of ZOLGENSMA contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Thrombocytopenia: Monitor platelet counts before ZOLGENSMA infusion, and weekly for the first month and then every other week for the second and third month until platelet counts return to baseline. (2.3, 5.2)
- Elevated Troponin-I: Monitor troponin-I before ZOLGENSMA infusion, and weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline. (2.3, 5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AveXis at 1 833-828-3947 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Pediatric use: Use of ZOLGENSMA in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until full-term gestational age is reached. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2019 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to July 31, 2019

1. Muscular Atrophy, Spinal	*2436*
2. Oligonucleotides, Antisense/	*9299*
3. nusinersen.mp	*114*
4. AVXS-101.mp	*7*
5. 2 or 3 or 4	*9405*
5. 1 and 5	*94*
6. limit 5 to (english language and humans	*79*

Appendix 3: Abstract from Randomized Clinical Trial

Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2018;378(7):625-635.
Background: Nusinersen is an antisense oligonucleotide drug that modulates pre–messenger RNA splicing of the survival motor neuron 2 (*SMN2*) gene. It has been developed for the treatment of spinal muscular atrophy (SMA).
Methods: We conducted a multicenter, double-blind, sham-controlled, phase 3 trial of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary end point was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 15 months of treatment; HFMSE scores range from 0 to 66, with higher scores indicating better motor function. Secondary end points included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score (≥3 points), an outcome that indicates improvement in at least two motor skills.
Results: In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points) and a least-squares mean decrease in the control group (by –1.9 points), with a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval, 3.7 to 8.1; P<0.001). This result prompted early termination of the trial. Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (P<0.001), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).
Conclusions: Among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group. (Funded by Biogen and Ionis Pharmaceuticals; CHERISH ClinicalTrials.gov number, NCT02292537opens in new tab.)

Onasemnogene abeparvovec (Zolgensma®)

Goal(s):

- Ensure utilization of onasemnogene abeparvovec in appropriate SMA (spinal muscular atrophy) populations with demonstrated efficacy.

Length of Authorization:

- Once in a lifetime dose

Requires PA:

- Onasemnogene abeparvovec

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the medication prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy such as pediatric neurologist?	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient less than 2 years of age?	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has the Spinal Muscular Neuropathy (SMA) diagnosis been confirmed to document the Spinal Motor Neuron (SMN)1 gene is missing or not functional by genetic documentation of : • Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); OR • Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 (allele 2) AND • Fewer than 4 copies of SMN2	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have advanced SMA* (complete paralysis of the limbs, permanent ventilator dependence)? *Note FDA label states efficacy has not been established in these patients	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 8
8. Has baseline motor ability been documented via: • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) OR • Assessment of motor function developmental milestones by physical therapist OR • Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score • Gross Motor Function Measure OR • Hammersmith Functional Motor Scale (HFMS) OR • Modified/Expanded Hammersmith Functional Motor Scale	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the child been screened for viral infection?	**Yes:** Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Is the baseline adeno-associate virus vector (AAV) 9 antibody titer < 1:50? Note: Efficacy has not been established in this population and high anti-AAV9 antibody titers are expected to limit efficacy of therapy.	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
11. Have the following labs been obtained: a.) a baseline platelet count AND b.) baseline liver function tests (AST, ALT, total bilirubin, and PT) AND c.) baseline troponin-I	**Yes:** Go to # 12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient currently receiving nusinersen?	**Yes:** Go to # 14	**No:** Go to # 15
14. Are there plans to discontinue nusinersen?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Is there attestation that the patient and provider will comply with case management required by the Oregon Health Authority? Case management includes follow-up assessment to assess treatment success, monitoring, and adverse events.	**Yes:** Approve for one time infusion	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19 (DM)
Implementation: TBD

Nusinersen

Goal(s):
- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:
- Up to 8 months for initial approval and up to 12 months for renewal.

Requires PA:
- Nusinersen (billed as a pharmacy or physician administered claim)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code. Go to #2	
2. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have type 1, 2 or 3 Spinal Muscular Atrophy documented by genetic testing and at least 2 copies of the SMN2 gene?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the patient ventilator dependent (using at least 16 hours per day on at least 21 of the last 30 days)? Note: This assessment does not apply to patients who require ventilator assistance	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5

Approval Criteria		
54. Is a baseline motor assessment available such as one of the following functional assessment tools: • Hammersmith Infant Neurological Examination (HINE-2) • Hammersmith Functional Motor Scale (HFSME) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • Upper Limb Module (ULM) • 6-Minute Walk Test	**Yes:** Go to #56	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient received onasemnogene abeparvovec (Zolgensma)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** For initial approval, approve 5 doses over 8 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's motor function improved as demonstrated by: • Improvement from baseline motor function score documented within one month of renewal request AND • More areas of motor function improved than worsened	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: *9/19 (DM); 7/17 (DM); 3/17*
Implementation: *TBD: 9/1/17; 5/17*

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Drug Class Update with New Drug Evaluation: Bone Metabolism Drugs

Date of Review: September 2019

Generic Name: romosozumab-aqqg

Date of Last Review: March 2018
Dates of Literature Search: January 2018- May 23, 2019
Brand Name (Manufacturer): Evenity™
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for a new monoclonal antibody (romosozumab) recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In addition, new comparative evidence for existing bone metabolism agents (e.g.; bisphosphonates, teriparatide, abaloparatide, zoledronic acid, and denosumab) for management of osteoporosis and Paget disease will be reviewed.

Research Questions:
- Is there new comparative evidence that bone metabolism agents differ in efficacy or effectiveness for osteoporosis?
- Is there any new comparative evidence the bone metabolism agents differ in harms?
- Are there specific subpopulations (gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?
- What is the evidence for efficacy and harms for the new monoclonal antibody, romosozumab, recently approved to treat postmenopausal osteoporosis**?**

Conclusions:
Class Update
- Four new systematic reviews were identified for inclusion in this drug class update.
- An updated systematic review for the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One large randomized clinical trial (RCT) comparing screening with no screening reported 28% reduction in hip fractures for women with screening (2.6% vs. 3.5%; hazard ratio [HR], 0.72; 95% Confidence Interval [CI] 0.59-0.89; Absolute Risk Reduction [ARR] 0.9%) but no other statistically significant benefits or harms were observed at 5 years' follow-up.[1] Moderate quality evidence showed that for women, bisphosphonates, parathyroid hormone, raloxifene, and denosumab were associated with a lower risk of vertebral fractures (9 trials; relative risks [RRs] from 0.32-0.64].[1] Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI 0.16 to 0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1]

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- A high quality systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] After 3 to 5 years of treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (based on radiographic evidence) only for zoledronate: low strength of evidence (SOE), clinical evidence only for alendronate (moderate SOE), but did not reduce nonvertebral fractures (low SOE).[2]
- A high quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] There was no significant difference between the risk of fracture (RR 1.13; 95% CI 0.82 to -1.55; P=0.466), adverse events [AEs], (RR 1.00; 95% CI 0.96 to 1.04; P=0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34 to 137; P=0.280) between bisphosphonates and denosumab in the meta-analysis.[3] Evidence from this meta-analysis suggests no benefit of denosumab for reducing risk of fracture over bisphosphonates.[3]
- Six studies were included in a high quality systematic review that evaluated the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37; 95% CI, 0.18 to 0.77; P=0.008), non-vertebral fracture (RR 0.79; 95% CI, 0.68 to 0.92; P<0.003,) and hip fracture (RR 0.59; 95% CI, 0.42 to 0.83; P=0.002) compared with placebo, alendronate and teriparatide at 24 months (moderate strength of evidence).[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00; 95% CI 0.98 to 1.02; p=0.93) over the 24 month study periods (moderate strength of evidence).[4] Absolute rates were not reported, refer to **Table 2** for a specific study results from the 4 Phase 3 trials with romosozumab.

Romosozumab

- The safety and efficacy of romosozumab were demonstrated in 2 clinical Phase 3 trials involving women with postmenopausal osteoporosis. One additional small Phase 3 trial evaluated the safety and efficacy of romosozumab in men with a history of fracture.
- In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, moderate quality evidence shows that romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo during the first 12 months of therapy (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]
- The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] Moderate quality evidence shows after 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] In this trial, serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients [1.9%]) during the first year of therapy.[6]
- The BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Moderate quality evidence demonstrates that after 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Incidence of fracture, the FDA recommended primary endpoint to assess osteoporosis therapy, was not evaluated in this small trial and romosozumab is not currently approved for use in men.
- In the FRAME and ARCH trials, the following adverse reactions that occurred in more than 2% of patients and were associated with romosozumab administration included arthralgia (13.0%), headache (5.8%) and injection site reactions (5.2%).[8]
- The romosozumab drug label has a black box warning regarding the possibility for increased the risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Patients with a history of myocardial infarction or stroke within the past year should not start on romosozumab therapy.[8]

- There is insufficient data for long-term safety and efficacy of romosozumab beyond 12 months of administration. Due to waning efficacy on bone development after 12 months, the FDA has limited duration of romosozumab therapy to 12 months.[8]

Recommendations:

- Maintain romosozumab as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical prior authorization (PA) criteria for bone metabolism agents to include romosozumab.
- Add denosumab to PA criteria for bone metabolism agents.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Abaloparatide was reviewed by the Pharmacy and Therapeutics Committee at the November 2017 meeting. Abaloparatide was designated as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP) and clinical prior authorization (PA) criteria for bone metabolism agents were updated to include abaloparatide. One systematic review which evaluated the use of bisphosphonates in men was presented to the committee was part of the 2017 class update. Moderate quality evidence shows that bisphosphonates reduce fracture risk for men with osteoporosis.[9] Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[9] The American College of Endocrinology (AACE/ACE) and American College of Physicians (ACP) recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line treatment options for postmenopausal osteoporosis in their clinical practice guidelines.[10,11] Preferred drugs on the PMPDP for osteoporosis include alendronate, ibandronate and risedronate. Nonpreferred drugs including raloxifene, denosumab, abaloparatide and teriparatide are subject to PA review. Most of the Oregon Health Plan (OHP) Fee-For-Service (FFS) utilization for bone metabolism drugs is due to oral alendronate. The PDL status of the bone metabolism agents is presented in **Appendix 1.**

Background:

Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength, and increased risk of fracture.[12] According to the World Health Organization (WHO) diagnostic classification, osteoporosis is defined by bone mineral density (BMD) at the hip or lumbar spine that is less than or equal to 2.5 standard deviations (SD) below the mean BMD of a young-adult reference population.[13] Major risk factors for osteoporosis are female gender, elderly age, low BMD, and low intake of calcium and vitamin D.[12] Medications that affect endocrine pathways may also cause secondary osteoporosis.[12] The largest risk group for osteoporosis is post-menopausal women. Although osteoporosis is more prevalent in women, it is estimated that up to one third of new osteoporotic fractures occur in men.[14] Some of the more common secondary causes of osteoporosis in men include glucocorticoid treatment, alcohol abuse, obstructive pulmonary disease, hypogonadism, post-transplantation, and androgen ablation therapy in prostate cancer.[15]

Bone fractures are the clinical consequence of osteoporosis. The most common fractures are those of the vertebrae, hip, and wrist.[12] Risk of fracture can be assessed with the Fracture Risk Assessment (FRAX) Tool, which estimates the 10-year probability of hip fracture and major osteoporotic fracture (spine or forearm) using 9 clinical risk factors including BMD.[16] Hip fractures result in disability related to difficulty with ambulation, inability to perform of activities of daily living, and are associated with increased nursing home and rehabilitation hospital admissions.[17] Approximately 20% of patients who experience hip fractures die within a year of injury.[12] Osteoporosis poses a heavy financial burden on patients, with annual direct medical costs estimated at 17 to 20 billion dollars in the United States.[18] By 2025, annual fractures and associated costs are projected to rise by almost 50%.[19] The most rapid growth in fracture risk is estimated for people 65-74 years of age.[19]

Adult bone is continuously remodeled by osteoclastic bone resorption and osteoblastic bone formation.[20] The drugs used to slow bone loss in osteoporosis are of two categories: anti-resorptive (osteoclast inhibition) and anabolic (osteoblast stimulation). Anti-resorptive agents include bisphosphonates (e.g., alendronate, ibandronate, risedronate, and zoledronic acid), selective estrogen receptor modulators (raloxifene), and a monoclonal antibody (denosumab). The parathyroid hormone analogs, teriparatide and abaloparatide are anabolic agents. The primary goal of osteoporosis management is to reduce fracture risk. Randomized clinical trials demonstrate a reduction of vertebral and hip fractures with bisphosphonates. Alendronate and risedronate also decrease vertebral fractures in men and in patients with glucocorticoid-induced osteoporosis.[21] The main concerns associated with bisphosphonate use are rare side-effects, such as atypical femur fractures and osteonecrosis of the jaw. Raloxifene has been shown to reduce the risk of vertebral, but not non-vertebral, fractures.[17] Although it reduces breast cancer risk, raloxifene increases the incidence of hot flashes and venous thromboembolism. Teriparatide decreases vertebral and nonvertebral fractures.[22] Teriparatide is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have high risk of fracture, and individuals whose condition has not improved with bisphosphonate therapy.[22] Due to an increase in the risk of osteosarcoma in growing rodents treated with high doses of teriparatide, the FDA limited the treatment duration with teriparatide to 24 months.[22] Denosumab has been shown to decrease hip, vertebral, and nonvertebral fractures compared with low doses of calcium and vitamin D.[21] Since denosumab is a biologic agent, its use is associated with elevated risk for serious infection. Denosumab can also have adverse effects on bone and calcium metabolism including hypocalcemia, atypical femoral fractures, and osteonecrosis of the jaw.[23] The recently approved osteoporosis medication, romosozumab, is a monoclonal antibody that binds to sclerostin, a regulatory bone factor in bone metabolism. The safety and efficacy of romosozumab is discussed in more depth later in this report.

The discovery of sclerostin as a key inhibitor of bone formation was made by investigators studying patients with 2 rare, genetic syndromes characterized by bone overgrowth and high bone mass; sclerosteosis and van Buchem disease.[24] Of note, individuals with sclerosteosis are resistant to bone fracture.[25] These findings stimulated interest in exploring the potential of antisclerostin therapy as a strategy to increase bone formation in patients with osteoporosis.[24] Sclerostin, a protein secreted by osteocytes, inhibits wingless-related integration (Wnt) signaling within osteoblasts thus decreasing osteoblast activity. The Wnt signaling pathway plays a significant role in skeletal development, adult skeletal homeostasis, and bone remodeling.[4] In addition, Wnt signaling is increasingly recognized for its involvement in vascular pathophysiology.[26] There is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification.[27]

Measurement of bone density at the hip and lumbar spine with Dual X-Ray Absorptiometry (DEXA) is a surrogate marker used to diagnose osteoporosis. As well as providing diagnostic information, low BMD is recognized as a major risk factor for fractures.[28] A meta-analysis of prospective cohort studies found that every 1 SD decrease in BMD at the femoral neck in women was associated with a relative risk of 2.6 (95% CI 2.0 to 3.5) for hip fracture and 1.6 (95% CI 1.4 to 1.8) for all fractures.[29] A 1 SD decrease in lumbar spine BMD was associated with a relative risk of 2.3 (95% CI 1.9 to 2.8) for vertebral fracture and 1.5 (95% CI 1.4 to 1.7) for all fractures.[29]

Bone density monitoring via DEXA can be used to monitor the effects of pharmacologic therapy. While there are a number of approaches to monitoring therapy, there is no consensus on the optimal approach.[30] The American College of Physicians (ACP) recommends against monitoring during therapy, as many women treated with antiresorptive therapy have a reduction in fracture even when BMD does not increase.[31] In general, stability or an increase in BMD is considered to be response to osteoporosis therapy. Significant BMD loss should result in an evaluation of factors contributing to suboptimal therapeutic effect (e.g. adherence) and an assessment of alternative treatment strategies. A minimal clinically important difference has not been identified for BMD.

Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis. A fragility fracture is a low-energy fracture that would not normally be expected to result in a broken bone, such as a fall from standing height or less. The most common fractures associated with

osteoporosis are vertebral (27%), wrist (19%), hip (14%), and pelvic (7%).[19] According to the FDA, radiographic vertebral fracture is the accepted primary endpoint for fracture trials supporting an osteoporosis indication.[27]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Screening and Treatment to Prevent Osteoporotic Fractures
A high quality systematic review from the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One hundred sixty-eight fair- or good-quality articles met inclusion criteria.[1] The accuracy of bone measurement tests or clinical risk assessments for identifying osteoporosis or predicting fractures varied from very poor to good.[1] Osteoporosis screening involves clinical fracture risk assessment, bone measurement testing via DEXA, or both.[1] One large, fair quality RCT comparing screening with no screening reported 28% reduction in hip fractures (2.6% vs. 3.5%; HR 0.72; 95% CI, 0.59-0.89; ARR 0.9%), but no other statistically significant benefits were observed at 5 years' follow-up (osteoporosis-related fractures, clinical fractures, or mortality).[1] This trial also assessed the effect of screening on anxiety and quality of life and found no differences between participants allocated to screening versus usual care (variance not reported , P< 0.10 for all outcomes).[1] Current evidence is insufficient to assess the balance of benefits and harms for screening for osteoporosis to prevent osteoporotic fractures in men.[1]

Moderate quality evidence showed that for women, bisphosphonates, teriparatide, raloxifene, and denosumab were associated with a lower risk of vertebral fractures compared to placebo (9 RCTs; relative risks from 0.32 to 0.64).[1] Bisphosphonates (8 RCTs, pooled RR 0.84; 95% CI 0.76-0.92) and denosumab (1 RCT, RR 0.80; 95% CI, 0.67-0.95) were associated with a lower risk of nonvertebral fractures.[1] Denosumab reduced the risk of hip fracture (1 RCT, RR 0.60; 95% CI, 0.37-0.97), but bisphosphonates did not have a statistically significant association with hip fracture reduction (3 RCTs, pooled RR 0.70; 95% CI, 0.44-1.11).[1] Absolute risk reduction was not reported. Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI, 0.16-0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1] Pooled analysis of 3 RCTs comparing raloxifene to placebo suggested a possible association of raloxifene with deep vein thrombosis, however the results were not significant (0.7% raloxifene vs. 0.3% placebo, RR 2.14; 95% CI, 0.99-4.66).[1] In summary, for women, screening to prevent osteoporotic fractures may reduce hip fractures, and treatment reduces the risk of vertebral and nonvertebral fractures. There was not consistent evidence of treatment harms.[1]

Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention

A good quality systematic review sponsored by AHRQ summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] Long-term osteoporosis drug therapy was defined as greater than 3 years and drug holidays were defined as discontinuation for 1 year or greater after 1 year or greater of medication use.[2] Sixty-one studies were included in the systematic review. No trials compared active treatments, sequential treatments, or different durations of drug holidays.[2] In addition, harms and controls were inconsistently defined.[2]

In women with osteoporosis, 4 years of alendronate reduced clinical fractures (HR 0.64; 95% CI 0.50-0.82; Absolute Risk Reduction [ARR]=7; Number Needed to Treat [NNT]=15; moderate SOE) and radiographic vertebral fractures (HR 0.50; 95% CI 0.31-0.82; ARR 3; NNT 34; moderate SOE), while 4 years of raloxifene reduced clinical vertebral fractures (relative risk 0.58; 95% CI 0.43-0.79; ARR=2; NNT=50; high SOE), but not hip (moderate SOE) or nonvertebral fractures (high SOE). In women with osteopenia or osteoporosis, 6 years of zoledronate reduced incident clinical fractures (HR 0.73; 95% CI 0.60-0.90; ARR=5; NNT=20; moderate SOE) and clinical vertebral fractures (HR 0.41; 95% CI 0.22-0.75; moderate SOE).[2] After 3 to 5 years of prior treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (radiographic only for zoledronate [low SOE], clinical only for alendronate [moderate SOE]), but did not reduce nonvertebral fractures (low SOE).[2] Hormone therapies increased cardiovascular events, mild cognitive impairment or dementia, and other harms.[2] Observational studies showed that long-term bisphosphonates may increase atypical femoral fractures (low SOE) and osteonecrosis of the jaw compared to placebo or no treatment (low SOE in 2 comparisons, insufficient in 1).[2]

Key messages include:

- Evidence on the effects of long-term osteoporosis drug treatment and drug continuation versus discontinuation is mostly limited to white, healthy, postmenopausal women.[2]
- Long-term alendronate reduces radiographic vertebral and nonvertebral fractures in women with osteoporosis; long-term zoledronate reduces vertebral and nonvertebral fractures in women with osteopenia or osteoporosis.[2]
- Long-term bisphosphonates may increase atypical femoral fractures and osteonecrosis of the jaw, although both are rare.[2]
- In women with osteoporosis, long-term raloxifene reduces vertebral fractures, but not hip or nonvertebral fractures, and increases venous thromboembolism.[2]
- Long-term oral hormone therapies reduce hip and clinical fractures but increase multiple serious harms.[2]
- Evidence is insufficient about the effects of long-term denosumab, risedronate, ibandronate, teriparatide, and abaloparatide on fractures and harms.[2]
- Continuing bisphosphonates after 3–5 years versus discontinuation reduces some measures of vertebral fractures, but not nonvertebral fractures.[2]

Denosumab Compared To Bisphosphonates to Treat Postmenopausal Osteoporosis

A good quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] Eleven studies with low risk of bias involving 5446 patients (denosumab = 2873, bisphosphonates = 2573) were included in the meta-analysis.[3] The publication years ranged from 2006 to 2016. Six studies were conducted in the USA, 2 in Canada, and one each in France, Spain, the United Kingdom and Australia.[3] The dose of denosumab was 60 mg via subcutaneous injection every 6 months. Four types of bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) were included. The duration of follow-up ranged from 12 to 24 months. There was no significant difference between the risk of fracture (risk ratio (RR), 1.13; 95% confidence interval (CI), 0.82 to -1.55; P = 0.466), adverse events (AEs; RR 1.00; 95% CI 0.96–1.04; P = 0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34–137; P = 0.280).[3] Current evidence suggested no benefit of denosumab for reducing risk of fracture compared to bisphosphonates.[3] More long-term follow-up RCTs are needed to identify the potential complications of denosumab.[3]

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Meta-Analysis of Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Six studies were included in a high quality systematic review that was conducted to evaluate the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] Two trials compared romosozumab with placebo, 3 trials compared romosozumab to teriparatide and 1 trial compared romosozumab to alendronate.[4] Three trials were Phase 2 studies and the other 3 were Phase 3 studies in women. Subjects were randomly assigned to receive subcutaneous (SC) injections of romosozumab 210 mg monthly for at least 12 months. Studies were graded as having low risk of bias using the Cochrane manual.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37, 95% CI 0.18–0.77, p=0.008), non-vertebral fracture (RR 0.79, 95% CI 0.68–0.92, p<0.003) and hip fracture (RR 0.59, 95% CI 0.68–0.92 p=0.002) compared with other therapies at 24 months.[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00, 95% CI 0.98–1.02; p=0.93) over the 24 month study period.[4] However, more data is needed to clarify the safety of romosozumab, particularly for cardiovascular events.

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[33-38]

New Guidelines: No new high quality guidelines were identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Denosumab	Prolia®	4/19	Warnings and Precautions	Hypocalcemia may be exacerbated by the use of Prolia®. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis, treatment with other calcium-lowering drugs), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of Prolia® injection. In some post marketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Randomized Controlled Trials:

A total of 109 citations were manually reviewed from the initial literature search. After further review, 109 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

The humanized monoclonal antibody romosozumab was FDA-approved April 2019 for treatment of osteoporosis in postmenopausal women with a high risk of fracture.[8] Romosozumab inhibits sclerostin, a protein secreted by osteocytes that blocks bone formation. As a result of romosozumab administration, bone formation is increased and bone resorption decreased. One 210 mg dose of romosozumab consists of two (105 mg) injections, one immediately following the other, given once a month by a health care professional.[8] Duration of romosozumab therapy is limited to 1 year because the bone-forming effect of the drug wanes after 12 doses.[8]

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The safety and efficacy of romosozumab were evaluated in 3 clinical trials involving women with postmenopausal osteoporosis and 1 trial in older men with previous fracture. FDA approval for romosozumab was based on 2 large Phase 3 trials, FRAME and ARCH.[27] The good quality FRAME trial was an international, randomized, double blind study in 7180 women with an average age of 71 years and mean T score at femoral neck of -2.7.[5] A small percentage (18%) of subjects had previous vertebral fracture at baseline.[5] Subjects received either romosozumab 210 mg subcutaneously (SC) once a month or placebo for 12 months followed by an additional 12 months of open label therapy with denosumab 60 mg SC every 6 months (to preserve the BMD gains with romosozumab) in both treatment groups.[5] All participants received daily calcium 500-1,000 mg and vitamin D 600-800 International Unit (IU) supplementation. The co-primary endpoints were the proportion of subjects with new vertebral fractures at 12 and 24 months.[5] Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) fractures and nonvertebral fractures.[5] During the first 12 months of therapy, romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] At 24 months, the rates of vertebral fractures remained lower in the romosozumab group than in the placebo group after each group made the transition to denosumab (0.6% in the romosozumab group vs. 2.5% in the placebo group, RR 0.75; 95% CI, 0.16 to 0.40; P<0.001; ARR 1.9%; NNT 53).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]

The good quality ARCH study compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] A total of 4093 women were enrolled in this study. The women enrolled in this trial were at much higher risk of fracture than the women in the placebo-controlled FRAME study. The average age of the study participants was 74 years, and more than half of the women were age 75 or older. Ninety-nine percent of the women had a history of a fragility fracture.[6] The co-primary endpoints of the study were the reduction in new vertebral fracture incidence at 24 months and the cumulative incidence of clinical fracture through the primary analysis period.[6] The primary analysis period ended when at least 330 subjects had a clinical fracture and all subjects had completed the 24-month visit; median time on study at time of primary analysis was 33 months.[6] Secondary endpoints included nonvertebral and hip fracture risk reduction at 24 months. After 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] Clinical (nonvertebral and symptomatic vertebral) fractures occurred in 9.7% of subjects in the romosozumab-to-alendronate group versus 13.0% in the alendronate-to-alendronate group, representing lower risk clinical fracture with romosozumab (RR 0.73; 95 CI 0.61 to 0.88; <0.001; ARR 3.3%; NNT 31).[6]

The fair quality STRUCTURE trial compared the effects of 12 months of romosozumab with teriparatide in women who were transitioning from bisphosphonate therapy.[39] Previous data suggest that the clinical benefit of teriparatide might be reduced in patients transitioning from bisphosphonates compared with bisphosphonate-naive patients.[39] This trial was a randomized, open-label assessment conducted in 436 postmenopausal women with osteoporosis at high risk for fracture.[39] The average age of subjects was 72 years and all the participants had experienced a previous fracture. The open-label study design was necessary due to the inability to mask the teriparatide pen. The primary endpoint was percentage change from baseline in total hip BMD after 12 months of therapy. The mean percentage change from baseline in total hip BMD was 2.6% in the romosozumab group and - 0.6% in the women who received teriparatide (mean difference (MD) 3.2%; 95% CI, 2.7 to 3.8; p<0.0001).[39] Fracture incidence, the primary endpoint recommended by the FDA for osteoporosis trials, was not evaluated in this trial. The findings from this trial suggest that romosozumab might be an effective treatment option for patients at increased risk for fracture who are transitioning from oral bisphosphonate therapy.[39]

The fair quality BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Subjects were randomized 2:1 to receive romosozumab 210 mg SC monthly or placebo for 12 months. The primary efficacy endpoint was percentage change from baseline in lumbar spine BMD at month 12. After 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Fracture incidence was not evaluated in this trial. Currently, romosozumab does not have FDA approval for use in men. More details about the study design of all 4 trials is summarized in **Table 5.**

Study Limitations:

The study population in the FRAME trial was not representative of the US population (only about 3% North American while about 40% were Latin American).[5] A total of 132 patients (1.8%) were from the United States. In addition, this study noted lower rates of non-vertebral fracture and lower FRAX scores in Latin American regions, which may have underestimated the non-vertebral rate in the placebo group.[27] The investigator attributes the lack of significance of the nonvertebral fracture reduction to a regional subgroup interaction in Central/Latin America where a lower than expected nonvertebral fracture rate in the placebo group was observed (assumed 3.5%, observed 1.2%).[27] The observed nonvertebral fracture rate was also lower than expected in the small enrolled population in North America (assumed 3.5%, observed 1.1%).[27] Thirdly, although romosozumab treatment decreased drastically the risk of vertebral fractures at 12 months, reductions of similar magnitude (61–65%) in such fractures have already been described after 1 year of treatment with anti-resorptive agents.[40] Finally, the 25% reduction in the incidence of nonvertebral fractures observed after 1 year of treatment with romosozumab, although clinically relevant, was not statistically significant.[40]

The FDA noted that reduction of clinical fractures is not an appropriate endpoint in the FRAME and ARCH trials because the term, clinical fracture, does not have clinical meaningfulness among healthcare professionals and can be subject to different interpretation in the labeling.[27] In addition, clinical fracture rates in the FRAME study are combined from nonvertebral fractures (85%) and clinical vertebral fractures (15%).[27] As nonvertebral fracture endpoints were not statistically significant, the incidence rate differences for clinical fractures in the romosozumab group compared to placebo are from clinical vertebral fractures which were already counted in the primary endpoint.[27]

A limitation of the STRUCTURE trial was the open-label study design, which was necessary because of the inability to mask the teriparatide pen. Although the treatment assignments were open label, the efficacy endpoints were objective measurements and assessed by investigators who were masked to treatment allocation.[39] Also, this study was not powered to assess the difference in fracture incidence between treatment groups, and fracture events were not adjudicated or confirmed.[39] Efficacy endpoints in the BRIDGE trial were intermediate (BMD changes) and did not include study fracture incidence after therapy in men.[27]

Clinical Safety:
In the FRAME trial, the incidence of nonfatal serious adverse events was 8.7% in the placebo group and 9.6% in the romosozumab group.[5] The most common adverse reactions reported with romosozumab (greater than or equal to 5% and at a higher incidence than placebo) were arthralgia and headache in both the FRAME and ARCH trials.[5] The most common adverse reaction leading to discontinuation of romosozumab was arthralgia (6 subjects [0.2%] in the placebo group and 5 subjects [0.1%] in the romosozumab group).[5] In the ARCH trial, the incidence of nonfatal serious adverse events was 13.3% in the alendronate group and 11.9% in the romosozumab group.[6] The percentage of patients who withdrew from the study due to adverse events was 1.2% in the alendronate group and 1.2% in the romosozumab group.[6] Adverse reactions occurring in greater than 2% of women treated with romosozumab compared to placebo are presented in **Table 3.**

Table 3. Adverse reactions occurring in ≥ 2% of romosozumab-treated women compared to placebo[8]

Adverse Reaction	Placebo (n=3576)	Romosozumab (n=3581)
Arthralgia	434 (12.1%)	468 (13.1%)
Headache	208 (5.8%)	235 (6.6%)
Muscle Spasms	140 (3.9%)	163 (4.6%)
Edema	67 (1.9%)	86 (2.4%)
Asthenia	79 (2.2%)	84 (2.3%)
Neck Pain	54 (1.5%)	80 (2.2%)
Insomnia	68 (1.9%)	72 (2.0%)
Paresthesia	62 (1.7%)	72 (2.0%)

The immunogenicity of romosozumab was evaluated using an immunoassay for the detection of anti-romosozumab antibodies.[8] Antibody formation against romosozumab occurred in 20% of patients on romosozumab and neutralizing capability occurred in 5% of patients with binding antibodies.[27] The presence of antibodies can reduce romosozumab exposure but do not appear to affect the effectiveness of romosozumab.[27]

Severe adverse events observed during clinical trials included osteonecrosis of the jaw (< 1%) and atypical fracture (<1%).[8] In the ARCH trial, serious cardiovascular events were observed more often with romosozumab than with alendronate (50 of 2,040 patients (2.5%) compared with 38 of 2,014 patients (1.9%); OR 1.31; 95% CI 0.85–2.00).[6] Sixteen patients (0.8%) treated with romosozumab had cardiac ischemic events compared with six (0.3%) treated with alendronate (OR 2.65; 95% CI 1.03–6.77).[6] Based on this data, the romosozumab drug label has a black box warning regarding the possibility for increased risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year.[8] If a patient experiences a myocardial infarction or stroke during therapy, romosozumab should be discontinued.[8]

Notably, the FRAME trial did not identify any imbalance in cardiovascular events in the romosozumab compared with the placebo groups.[5] The differences in adverse effects may be due to differences in the patient populations studied in the FRAME and ARCH trial. Women in the ARCH study were, on average, 4 years older than those enrolled in the FRAME trial. In addition, 96% of women in the ARCH trial had a prevalent vertebral fracture compared with only 18% of women in the FRAME trial. As osteoporotic fractures are associated with other ageing co‑morbidities, including cardiovascular disease, women in the ARCH trial may have been less healthy than the women in the FRAME trial.[27]

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Percentage of patients with new vertebral fractures
2) Percentage of patients with new non-vertebral fractures
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of patients with new vertebral fractures at 12 and 24 months

Table 4. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Sclerostin inhibitor which increases bone formation
Bioavailability	81%
Distribution	Volume of distribution: 3.92 Liters
Elimination	Monoclonal antibody unlikely to be filtered by the kidney or excreted in urine
Half-Life	12.8 days after 3 doses every 4 weeks
Metabolism	Metabolic pathway has not been characterized

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Cosman F, et al.[5] FRAME Phase 3 RCT, DB, PC, MC, PG N=7180	1. Romosozumab 210 mg SC monthly for 12 months followed by OL denosumab 60 mg SC every 6 months for 12 months 2. Placebo SC monthly for 12 months followed by OL denosumab 60mg SC every 6 months for 12 months	Demographics: 1. Mean age: 71 yo 2. Mean T-score at lumbar spine and femoral neck: -2.7 3. Previous vertebral fracture at baseline: 18% 4. Previous nonvertebral fracture: 22% 5. Ethnic group: -Hispanic 40% -Non-Hispanic 60% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo 2. Total hip or femoral neck BMD T-score between -2.5 and -3.5 Key Exclusion Criteria: 1. Total hip or femoral neck T-score ≤ 3.5 2. Previous hip fracture or more than 2 vertebral fractures 3. History of metabolic bone disease 4. Osteonecrosis of the jaw 5. Vitamin D level < 20 ng/ml 6. Current use of medications that affect bone metabolism	ITT: 1. 3589 2. 3591 PP: (completed 12-mo DB period) 1. 3185 2. 3205 Attrition: 12 mos- 1. 404 (11%) 2. 386 (11%) 24 mos- 1. 595 (17%) 2. 559 (16%)	Co-Primary Endpoints: 1. Percentage of patients with new vertebral fractures at 12 mos 1. 16 (0.5%) 2. 59 (1.8%) RR 0.27 (95% CI 0.16 to 0.47) P<0.001 2. Percentage of patients with new vertebral fractures at 24 mos 1. 21 (0.6%) 2. 84 (2.5%) RR 0.25 (95% CI 0.16 to 0.40) P<0.001 Secondary Endpoints: 1. Percentage of patients with new nonvertebral fractures at 12 mos 1. 56 (1.6%) 2. 75 (2.1%) HR 0.75 (95% CI 0.53 to 1.05) p=0.10 2. Percentage of patients with new nonvertebral fractures at 24 mos 1. 96 (2.7%) 2. 129 (3.6%) HR 0.75 (95% CI 0.57 to 0.97) p=0.06	1.3%/77 1.9%/53 NS NS	TEAEs at 12 mos 1. 2806 (78.4%) 2. 2850 (79.7%) SAEs at 12 mos 1. 344 (9.6%) 2. 312 (8.7%) Drug discontinuation due to AE at 12 mos 1. 103 (2.9%) 2. 94 (2.6%) Injection Site Reactions 1. 187 (5.1%) 2. 104 (2.9%) CV events 1. 46 (1.3%) 2. 46 (1.3%) Death 1. 29 (0.8%) 2. 23 (0.6%) 95% CI and p value NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified by age (<75, ≥75yo) and prevalent vertebral fracture. Baseline characteristics similar in both arms. Performance Bias: Low. Placebo presented in identical containers and stored/packaged the same as romosozumab. Detection Bias: Low. Patients, investigators, and sponsors blinded to initial treatment assignment. Central radiologic facility used for fracture assessment, DEXA and CT readings. Radiologists unaware of treatment assignments. Attrition Bias: Low. Similar attrition rates in both arms noted at 12 and 24 months. Reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple-imputation approach used to handle missing data. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Amgen and UCB Pharm designed the trial and Amgen was responsible for trial oversight. Several authors received grant support from Amgen. **Applicability**: Patient: The study population was not representative of the US population in postmenopausal women with osteoporosis. Small percentage of subjects had previous vertebral fracture at baseline. Intervention: Romosozumab dose was proven to be efficacious in Phase 2 trial. Comparator: Would be more informative to compare romosozumab with bisphosphonate. Outcomes: Cumulative incidence of new vertebral fractures is a reasonable endpoint to assess treatment effect. Setting: 222 centers in 25 countries: Central/Latin America: 43% Central/Eastern Europe: 29% Western Europe, Australia, New Zealand: 14% Asia/Pacific: 12% North America: 3%

2. Saag KG, et al.[41] ARCH trial Phase 3 RCT, DB, MC N=4093	1. Romosozumab 210 mg SC once monthly for 12 months followed by OL alendronate 70 mg orally once weekly 2. Alendronate 70 mg orally once weekly followed by OL alendronate 70 mg orally once weekly	Demographics: 1. Mean age: 74 yo 2. Mean T-scores: -Lumbar spine: -2.96 -Total hip: -2.80 -Femoral neck: -2.90 3. Ethnic group: -Non-Hispanic: 68 % -Hispanic: > 32% 4. Previous fracture: 99% Key Inclusion Criteria: 1. Postmenopausal women aged 55 to 90 yo with total hip or femoral neck BMD T-score ≤ -2.5 and at least one moderate or severe vertebral fracture OR T-score ≤ -2.0 with either ≥ 2 moderate to severe vertebral fractures or a fracture of the proximal femur 3-24 mos before randomization Key Exclusion Criteria: 1. Severe metabolic or bone disease 2. Current use of bone metabolism agents 3. Cr Cl < 35 ml/min	ITT: 1. 2046 2. 2047 PP: (completed study through primary analysis) 1. 1574 2. 1576 Attrition at 12 mos: 1. 215 (11%) 2. 224 (11%)	Co-primary Endpoints: 1. Cumulative incidence of new vertebral fracture at 24 months 1. 127 (6.2%) 2. 243 (11.9%) RR 0.50 (95% CI, 0.40 to 0.66), P<0.001 2.Cumulative incidence of new clinical (nonvertebral fracture and clinical vertebral fracture) fracture through primary analysis period (> 24 mos) 1. 198 (9.7%) 2. 266 (13%) HR 0.73 (95% CI 0.61 to 0.88), P<0.001 Secondary Endpoints: 1. Cumulative incidence of new vertebral fracture at 12 months 1. 82 (4.0%) 2. 128 (6.3%) RR 0.63 (95% CI, 0.47 to 0.85), P=0.003 2. Incidence of nonvertebral fracture at 12 months 1. 70 (3.4%) 2. 95 (4.6%) RR 0.74 (95% CI 0.54 to 1.01) P=0.057 3. Incidence of hip fracture at 12 months 1. 14 (0.7%) 2. 22 (1.1%) RR 0.64 (95% CI 0.3 to 1.26 P=0.19	5.7%/18 3.3%/31 2.3%/44 NS NS	TEAEs at 12 mos 1. 1544 (76%) 2. 1584 (79%) SAEs at 12 mos 1. 262 (13%) 2. 278 (14%) SAEs leading to drug discontinuation at 12 mos 1. 70 (3.4%) 2. 64 (3.2%) Injection Site Reaction at 12 mos 1. 90 (4.4%) 2. 53 (2.6%) Death 1.30 (1.5%) 2. 21 (1.0%) CV Events at 12 mos 1. 50 (2.5%) 2. 38 (1.9%) OR 1.31 (95% CI 0.85 to 2.00) P value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified according age (<75 yo vs. ≥75 yo). Baseline demographics balanced between groups. Performance Bias: Low. Subjects received a matched oral placebo or matched subcutaneous placebo depending on treatment assignment to maintain blinding. Detection Bias: Low. Patients, outcome assessors, health care providers, data collectors, and data analysts blinded to treatment assignment. All DEXA scan data submitted electronically to the central imaging vendor for analysis. Attrition Bias: Low. 11% of subjects withdrew from the trial, reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple imputation used for missing fracture status. Reporting Bias: Low. Protocol available online Other Bias: Unclear. Funded by Amgen. Amgen and UCB Pharma designed the trial, and Amgen was responsible for trial oversight and data analyses per a prespecified statistical analysis plan. An external independent data monitoring committee monitored unblinded safety data. **Applicability**: Patient: Women at high risk for fracture were included in the trial – 99% of subjects had a previous fracture. Intervention: Romosozumab dose evaluated in Phase 2 trials. Comparator: Bisphosphonate therapy is standard of care to manage osteoporosis. Outcomes: Incidence of vertebral fracture is an established endpoint for evaluating osteoporosis therapy. Setting: 125 centers: Central or Eastern Europe: 40% Latin America: 34% Western Europe, Australia, New Zealand: 13% Asia-Pacific or South Africa: 11% North America: 2%

3. Langdahl BL, et al.[39] STRUCTURE trial Phase 3 trial, OL, MC, PG N=436	1. Romosozumab 210 mg SC once monthly 2. Teriparatide 20 mcg SC once daily	Demographics: 1. Mean age: 72 yo 2. Mean baseline BMD T-score: -Total hip: -2.2 -Lumbar spine -2.9 -Femoral neck -2.4 3. Average duration of bisphosphonate therapy: 6.2 years 4. Ethnic group: -White: 89% -Other: 11% 5. Previous fracture: 100% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo with osteoporosis (T-score ≤ -2.5 at total hip, lumbar spine, femoral neck) and history of fracture after age 50 previously treated with bisphosphonate therapy for minimum of 3 years Key Exclusion Criteria: 1. Use of osteoporosis agents other than bisphosphonates 2. Vitamin D level < 50 nmol/L 3. History of metabolic or bone disease 4. Hyper- or hypocalcemia 5. Uncontrolled hyper- or hypothyroidism	ITT: 1. 218 2. 218 PP: 1. 198 2. 200 Attrition: 1. 20 (9%) 2. 18 (8%)	Primary Endpoint: Mean percentage change from baseline in total hip BMD at 12 months 1. 2.6% 2. -0.6% MD 3.2% (95% CI 2.7 to 3.8) p<0.0001 Secondary Endpoints: 1. Percent change from baseline in femoral neck BMD at 12 months 1. 3.2% 2. -0.2% MD 3.4% (95% CI NR) p<0.0001 2. Percent change from baseline in lumbar spine BMD at 12 months 1. 9.8% 2. 5.4% MD 4.4% (95% CI NR) p<0.0001	NA NA NA	SAEs 1. 17 (8%) 2. 23 (11%) SAEs leading to drug discontinuation 1. 6 (3%) 2. 12 (6%) Hypercalcemia 1. 2 (<1%) 2. 22 (10%) Arthralgia 1. 22 (10%) 2. 13 (6%) Injection Site Reaction 1. 17 (8%) 2. 6 (3%) Death 1. 1 (< 1%) 2. 1 (< 1%) P value and 95% CI NR		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Baseline demographics similar in both treatment groups. Performance Bias: High. Open label study due to inability to conceal teriparatide pen formulation. Patients assigned to teriparatide self-injected the study medication while patients assigned to romosozumab were administered the medication by HCPs. Detection Bias: Unclear. Investigators assessing efficacy endpoints were masked to treatment assignment. Attrition Bias: Low. Similar rates of study withdrawal in both arms with similar reasons for discontinuation. Reporting Bias: Low. Protocol is available at European Clinical Trial Register. Other Bias: Unclear. Funded by Amgen, Astellas, and UCB Pharma. Amgen and UCB Pharma designed the study in collaboration with external investigators. Amgen was responsible for study monitoring, oversight, and statistical analysis. A significant percentage of contributing authors received financial support from Amgen or were employed by Amgen. **Applicability**: Patient: Patients at high risk for fracture; primarily European, exposed to bisphosphonate therapy for 3 years with history of fracture. Intervention: Dose of romosozumab evaluated in Phase 2 trials Comparator: Teriparatide is a bone forming agent with a different MOA from romosozumab. Clinical benefit of teriparatide may be reduced by prior bisphosphonate therapy. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence after therapy due to inadequate power to assess differences in fracture rate. Setting: 46 sites in North America (7%), Latin America (18%), and Europe (75%)

4. Lewiecki EM, et al.[7] BRIDGE trial Phase 3 RCT, MC, DB, PC N=245	1. Romosozumab 210 mg SC once monthly for 12 months 2. Placebo SC once monthly for 12 months	Demographics: 1. Mean age: 72 yo 2. Baseline lumbar spine T-score: -2.3 3. Previous fracture: 54% 4. Ethnic group: White: 74% Asian: 11% Other: 15% Key Inclusion Criteria: 1.Men aged 55 to 90 yo with T-score ≤ -2.5 at the spine or hip or ≤ 1.5 at the spine or hip with a history of nonvertebral or vertebral fractures after age 45 Key Exclusion Criteria: 1. T-score ≤ -3.50 at the hip 2. History of hip fracture 3. History of metabolic or bone disease 4. Current use of medications that affect bone metabolism	ITT: 1. 163 2. 82 PP: 1. 152 2. 79 Attrition: 1. 11 (7%) 2. 3 (4%)	Primary Endpoint: Percent changes from baseline in lumbar spine BMD at 12 months 1. 12.1% 2. 1.2% P<0.001 95% CI NR Secondary Endpoints: 1. Percent change from baseline in DXA BMD at total hip at 12 months 1. 2.5% 2. -0.5% P<0.001 95% CI NR 2. Percent change from baseline in DXA BMD at femoral neck at 12 months 1. 2.2% 2. -0.2% P<0.001 95% CI NR	NA NA NA	TEAEs at 12 mos 1. 123 (76%) 2. 65 (80%) SAEs 1. 21 (12.9%) 2. 10 (12.3%) SAE leading to drug discontinuation 1. 5 (3.1%) 2. 1 (1.2%) Injection Site Reactions 1. 9 (5.5%) 2. 3 (3.7%) CV events 1. 8 (4.9%) 2. 2 (2.5%) p-value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to receive romosozumab or placebo via IVRS. Stratified by geographic region. Baseline demographics balanced between groups. Performance Bias: Low. Matched placebo given to subjects in the placebo arm. Detection Bias: Low. BMD measurements analyzed by a central imaging vendor. Attrition Bias: Low. Similar attrition rates in both arms. Reporting Bias: Low. Protocol available at ClinicalTrials.gov Other Bias: Unclear. Amgen Inc., UCB Pharma and Astellas Pharma provided financial support for this trial. The authors all report grant support from Amgen and UCB Pharma. **Applicability**: Patient: Primarily studied in Europe (66%) with relatively few participants in North America (9%). Applies to older men with 54% having a previous fracture. Intervention: Modeled after FRAME trial, as Phase 2 trials did not include men. Comparator: Would be more informative to compare romosozumab to standard of care (bisphosphonate) approved to treat osteoporosis in men. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence. Setting: 31 centers in Europe (66%), Latin America (14%), Japan (11%) and North America (9%)

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMD = bone mineral density; CI = confidence interval; CV = cardiovascular; DB = double blind; DEXA = dual-energy x-ray absorptiometry; HCP = health care professional; HR = hazard ratio; ITT = intention to treat; IVRS = interactive voice-response system; MC = multi-center; MD = mean difference; mITT = modified intention to treat; MOA = mechanism of action; Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NR = not reported; NNT = number needed to treat; OL = open label; OR = odds ratio; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; RR = risk ratio; SAE = serious adverse event; SC = subcutaneous; SEAs = serious adverse effects; TEAE = treatment emergent adverse effects; YO = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
alendronate sodium	ALENDRONATE SODIUM	TABLET	PO	Y
alendronate sodium	FOSAMAX	TABLET	PO	Y
ibandronate sodium	BONIVA	TABLET	PO	Y
ibandronate sodium	IBANDRONATE SODIUM	TABLET	PO	Y
risedronate sodium	ACTONEL	TABLET	PO	Y
risedronate sodium	RISEDRONATE SODIUM	TABLET	PO	Y
abaloparatide	TYMLOS	PEN INJCTR	SQ	N
alendronate sodium	ALENDRONATE SODIUM	SOLUTION	PO	N
alendronate sodium	BINOSTO	TABLET EFF	PO	N
alendronate sodium/vitamin D3	FOSAMAX PLUS D	TABLET	PO	N
calcitonin,salmon,synthetic	CALCITONIN-SALMON	SPRAY/PUMP	NS	N
calcitonin,salmon,synthetic	MIACALCIN	VIAL	IJ	N
denosumab	PROLIA	SYRINGE	SQ	N
etidronate disodium	ETIDRONATE DISODIUM	TABLET	PO	N
ibandronate sodium	BONIVA	SYRINGE	IV	N
ibandronate sodium	IBANDRONATE SODIUM	SYRINGE	IV	N
raloxifene HCl	EVISTA	TABLET	PO	N
raloxifene HCl	RALOXIFENE HCL	TABLET	PO	N
risedronate sodium	ATELVIA	TABLET DR	PO	N
risedronate sodium	RISEDRONATE SODIUM DR	TABLET DR	PO	N
teriparatide	FORTEO	PEN INJCTR	SQ	N
denosumab	XGEVA	VIAL	SQ	
ibandronate sodium	IBANDRONATE SODIUM	VIAL	IV	
pamidronate disodium	PAMIDRONATE DISODIUM	VIAL	IV	
zoledronic ac/mannitol/0.9NaCl	ZOLEDRONIC ACID	PIGGYBACK	IV	
zoledronic acid	ZOLEDRONIC ACID	VIAL	IV	
zoledronic acid	ZOMETA	VIAL	IV	
zoledronic acid/mannitol-water	RECLAST	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOMETA	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PIGGYBACK	IV	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 23, 2019

1.	Paget Disease, Extramammary/ or Pagets disease.mp.	6843
2.	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	73213
3.	Risedronate Sodium/	1146
4.	Alendronate/	3547
5.	ibandronate.mp.	869
6.	Etidronic Acid/	2714
7.	calcitonin/	15604
8.	Raloxifene Hydrochloride/	2560
9.	Teriparatide/	1813
10.	Denosumab/	1364
11.	Zoledronic acid.mp.	3905
12.	Pamidronate.mp.	2816
13.	Abaloparatide.mp	53
14.	Romosozumab	90
15.	1 or 2	79425
16.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	32101
17.	limit 16 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	109

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EVENITY safely and effectively. See full prescribing information for EVENITY.

EVENITY™ (romosozumab-aqqg) injection, for subcutaneous use
Initial U.S. Approval: 2019

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

----------INDICATIONS AND USAGE----------
EVENITY is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. (1)

Limitations of Use: Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Two separate subcutaneous injections are needed to administer the total dose of 210 mg. Inject two syringes, one after the other. (2.1)
- Should be administered by a healthcare provider. (2.1)
- Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm. (2.2)
- Adequately supplement calcium and vitamin D during treatment. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 105 mg/1.17 mL solution in a single-use prefilled syringe. A full dose of EVENITY requires two single-use prefilled syringes. (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4)
- Known hypersensitivity to EVENITY (4)

----------WARNINGS AND PRECAUTIONS----------
- Major Adverse Cardiac Events (MACE): Monitor for symptoms of MI and stroke and seek prompt medical attention if symptoms occur. (5.1)
- Hypersensitivity: Hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Discontinue EVENITY if a clinically significant allergic reaction occurs. (5.2)
- Hypocalcemia: Adequately supplement calcium and vitamin D during treatment with EVENITY. (5.3)
- Osteonecrosis of the Jaw: Monitor for symptoms. Consider discontinuation of therapy based on benefit-risk assessment. (5.4)
- Atypical Femoral Fracture: Evaluate new or unusual thigh, hip, or groin pain to rule out an incomplete femur fracture. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported with EVENITY in clinical trials were arthralgia and headache. (6.1)

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: Patients with severe renal impairment or receiving dialysis are at greater risk of developing hypocalcemia. Monitor serum calcium and supplement with calcium and vitamin D. (5.3, 8.7)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2019

Appendix 4: Key Inclusion Criteria

Population	Post-menopausal women at risk for fracture (Total hip or femoral neck T-score between -2.5 and -3.5)
Intervention	Romosozumab 210 mg SC once a month for 12 months
Comparator	Placebo, teriparatide, alendronate
Outcomes	Percentage of women experiencing new vertebral fracture
Timing	1-2 years
Setting	Primarily Europe and Latin America

Bone Metabolism Agents

Goal(s):

To ensure appropriate drug use and safety of bone metabolism ~~resorption suppression~~ agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Note: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed an oral bisphosphonate (alendronate, risedronate, or ibandronate) or do they have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh; deny and recommend trial of oral bisphosphonate
5. Is the request for denosumab?	**Yes:** Go to # 6	**No:** Go to # 7
6. Is denosumab being prescribed for one of the following reasons: • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Treatment to increase bone mass in men with osteoporosis at high risk for fracture • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer	**Yes:** Go to # 8	**No:** Pass to RPh; Deny; medical appropriateness
~~6.~~7. Is the request for raloxifene?	**Yes:** Go to #~~8~~6	**No:** Go to #~~9~~7
~~7.~~8. Is the patient pregnant, or for raloxifene requests, at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and for raloxifene: boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months

Approval Criteria		
~~8.~~9. Is the request for teriparatide and is the patient at high risk for fracture? Examples include: • Postmenopausal women with osteoporosis and T-score ≤ - 2.5 or history of fracture • Men with primary or hypogonadal osteoporosis* • Men or women with osteoporosis associated with sustained systemic glucocorticoid therapy	**Yes:** Go to #120	**No:** Go to #10~~8~~
~~9.~~10. Is the request for abaloparatide and is the patient a postmenopausal woman aged 49 to 86 years with osteoporosis at high risk for fracture? Inclusion criteria from the ACTIVE[1] trial: • Women with T score between - 2.5 and -5.0 AND radiologic evidence of vertebral fracture or history of nonvertebral fracture within the past 5 years OR • Women aged 65 years or older with T score between -3.0 and -5.0 without history of fracture OR T score between -2.0 and 5.0 with history of fracture.	**Yes:** Go to #11~~9~~	**No:** Go to #131
~~10.~~11. Has the patient received treatment with anticonvulsants that affect Vitamin D metabolism (phenobarbital, phenytoin, carbamazepine or primidone) or with chronic heparin within the past 6 months OR has the patient received daily treatment with oral, intranasal, or inhaled corticosteroids in the past 12 months?	**Yes:** Pass to RPh. Deny; medical appropriateness. (These patients were excluded from the ACTIVE[1] trial)	**No:** Go to #120.

Approval Criteria		
~~11.~~12. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated. Teriparatide and abaloparatide are only FDA approved for a total duration of therapy of 2 years.)
~~12.~~13. Is the request for romosozumab and is the patient a postmenopausal women with osteoporosis and T-score ≤ -2.5 or history of fracture?	**Yes:** Go to # 14	**No:** Go to # 15
~~13.~~14. Has the patient had a myocardial infarction or stroke within the past year?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months maximum.* *Note: FDA has only approved use of romosozumab for a total of 12 months. If continued osteoporosis therapy is warranted, continue therapy with an anti-resorptive agent (e.g. bisphosphonates, denosumab, or raloxifene).
~~14.~~15. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *7/19 (DM); 3/18; 7/16; 9/10*
Implementation: *TBD; 4/16/18; 8/16, 1/1/11*

** FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab.*

1. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA.316 (7):722-733.

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Drug Class Review with New Drug Evaluation: Targeted Therapies for Fabry Disease

Date of Review: September 2019
Generic Name: agalsidase beta, migalastat

End Date of Literature Search: 06/25/2019
Brand Name (Manufacturer): Fabrazyme® (Genzyme)
Galafold™ (Amicus Therapeutics)
Dossiers Received: No

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat patients with Fabry disease.

Research Questions:
1. What is the comparative efficacy and effectiveness for agalsidase beta and migalastat in treating Fabry disease?
2. What are the comparative harms for agalsidase beta and migalastat in treating Fabry disease?
3. Are there subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for Fabry disease is more effective or associated with fewer adverse events?

Conclusions:
<u>Agalsidase beta</u>
- The first published trial evaluating the efficacy of agalsidase beta was a randomized, double blind, placebo-controlled trial in 58 patients with Fabry disease.[1] The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of Gb3 were cleared (reduced to normal or near-normal levels) over 20 weeks.[1] The FDA reviewers noted that accumulation of Gb3 within capillary endothelial cells is not a disease feature that is routinely assessed by physicians and validated for a relationship to clinically discernable consequences.[2] Thus, Gb3 accumulation does not constitute a clinically meaningful endpoint, and effects on intracellular Gb3 accumulation should not be regarded as substantial evidence of clinical efficacy.[2] It is also unknown which phase of the disease may be most amenable to demonstrating a clinical impact of treatment; so it is unknown if the most sensitive portion of the disease population was being studied in this first trial to evaluate the efficacy of agalsidase beta.[2] Low quality evidence showed treatment with agalsidase beta resulted in clearance of Gb3 renal deposits in 20 of 29 (69%) treated patients compared with no changes in the placebo group (OR=0, p<0.001).[1] However, no improvements in symptoms or renal function were observed by the end of the 20 week trial.[1]
- The objective of a subsequent randomized, placebo-controlled clinical trial was to evaluate the effect of agalsidase beta on disease progression in a composite analysis of renal, cerebrovascular, and cardiac events in patients with advanced Fabry disease over 18 months.[3] Moderate quality evidence showed 42% (n=13) of the 31 patients in the placebo group and 27% (n=14) of the 51 patients in the agalsidase beta group experienced composite clinical events including reduced renal function, cardiac events, stroke, or death (hazard ratio [HR] 0.47; 95% CI, 0.21 to 1.03; P=0.06), but the results

were not statistically signficant.[3] Individual assessments of each outcome (decreased renal function and incidence of cardiac and cerebrovascular events) were not significantly different between patients in agalsidase beta and placebo groups.[3]

- Criteria for starting and stopping agalsidase alpha or agalsidase beta for Fabry disease are described in the United Kingdom (U.K.) Adult Fabry disease 2013 Standard Operating Procedures.[4] The U.K. procedures recommend that people with classical Fabry disease start enzyme replacement therapy (ERT) at diagnosis, and people with non-classical Fabry disease start ERT when disease symptoms have an impact on quality of life or there is evidence of renal disease, cardiac disease, neurovascular disease or gastrointestinal symptoms.[4]
- There is insufficient evidence for the effectiveness of agalsidase in delaying the onset or reducing the incidence and severity of Fabry disease-related complications, and its impact on long-term survival remains unclear.

<u>Migalastat</u>

- The National Institute of Health and Care Excellence (NICE) committee concluded that Fabry disease is a serious condition with a major effect on quality of life.[5] NICE guidelines recommend migalastat as an option for treating Fabry disease in people over 16 years of age with an amenable mutation and whose disease meets the existing starting criteria for ERT treatment.[5] NICE has not evaluated agalsidase beta for treating Fabry disease.[5] The authors of the NICE evidence review for migalastat concluded the studies providing clinical effectiveness evidence for this drug are limited and there are concerns about the design of the randomized controlled trials and the related open-label extension studies.[5] These concerns included: small populations and short trial durations, imbalances in patient baseline characteristics between the trial arms, and uncertainty as to how long individual patients had received migalastat because it was not reported how many patients were recruited to the open-label extension study from each arm of the initial study.[5]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of migalastat in treating Fabry disease if the following criteria are met:
    - Patients have an amenable mutation and are otherwise eligible for ERT for the treatment of Fabry disease.[6]
    - Migalastat is not to be used concomitantly with ERT.[6]
    - Patients must be under the care of a clinician experienced in the diagnosis and management of Fabry disease.[6]
- The FDA approval of migalastat was based on data from a phase 3 study in 67 treatment-naïve patients with Fabry disease.[7] The primary efficacy outcome was a surrogate endpoint to evaluate the proportion of patients with 50% or greater reduction in the average number of GL-3 inclusions per kidney interstitial capillary (KIC) in biopsy samples from baseline to month 6.[7] Moderate quality evidence from the intention-to-treat (ITT) population analysis did not show a significant treatment effect. A response was achieved in 13 of 34 (38%) migalastat-treated patients compared to 9 of 33 (27%) placebo-treated patients ($p = 0.3$).[7] In the ITT-amenable population with available histology data 13 of 25 (52%) patients on migalastat achieved the primary efficacy outcome compared to 9 of 20 (45%) patients on placebo (statistical data not reported).[7]
- Published data are not yet available on the effects of migalastat in patients with more advanced disease and with duration of therapy beyond 2 years.[8] There is insufficient data regarding the clinical outcomes of migalastat therapy.

Recommendations:

- Designate agalsidase beta and migalastat as non-preferred agents on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria for the Fabry disease treatments to ensure use according to FDA-approved indications (**Appendix 3**).
- Review costs in executive session.

Background:
Fabry disease is an inherited, X-linked, lysosomal storage disorder caused by mutations in the galactosidase alpha (GLA) gene, which leads to a deficiency in the enzyme alpha-galactosidase A (AGAL-A).[9] In the glycosphingolipid catabolic pathway, AGAL-A breaks down Gb3, a molecule containing 3 sugars attached to a fatty substance.[10] The deficiency of AGAL-A enzyme causes a progressive accumulation of glycosphingolipids in the lysosomes of multiple organs, which results in cellular dysfunction, tissue remodeling, and progressive organ damage.[11] More than 350 Fabry disease mutations have been identified. Males are more frequently and more severely affected than females, and symptoms are observed at a younger age in boys.[11] As many as 70% of carrier women experience symptoms of the disease, although the clinical manifestations of the disease are generally later in onset and milder in female carriers than in affected males.[12] Fabry disease is a panethnic condition with no racial or ethnic predilection.[13] Given the location of the GLA gene on the X chromosome, an affected male inherits the disease from his mother and can pass it to his daughters only.[11] Female carriers have a 50 percent chance of passing the gene on to daughters or sons.[11] The estimated incidence of Fabry disease is approximately 1 in 40,000 male births.[14] However, recognition of later-onset variants suggest the disease occurs more frequently than previously reported, perhaps up to 1 in 3,100 births.[14] Studies have also found an increased incidence of Fabry disease in dialysis patients, patients with cryptogenic strokes, and patients with hypertrophic cardiomyopathy with frequencies ranging from 1:20 to 1:1000 patients.[13] Fabry disease is a funded condition on line 60 (metabolic disorders) of the Health Evidence Review Commission (HERC) prioritized list of health services.[15]

Fabry disease has a spectrum of disease severity ranging from severe, early-onset disease (classic Fabry disease) to later-onset, milder disease (late-onset Fabry disease) to asymptomatic individuals (some heterozygous females).[8] Clinical presentation of Fabry disease is quite varied, and even within one family considerable variation is seen in the age of onset, rate of progression, and organ manifestations.[9] Fabry disease usually presents in childhood (5-9 years of age) with symptoms such as peripheral neuropathy, angiokeratomas (reddish-purple skin lesions) in the trunk area, abdominal pain, nausea, postprandial diarrhea and poor growth.[9] Decreased sweating (hypohidrosis) is another common problem, which has been attributed to effects on the sweat glands and autonomic nervous system.[9] More than 50% of men and 25% of women with Fabry disease have reported decreased sweating, heat intolerance, or both, in childhood.[9] Ocular involvement is most prominent in the cornea, lens, conjunctiva, and retina.[16] A characteristic corneal opacity, observed only by slit-lamp microscopy, is found in affected males and in most heterozygous females.[16] Neuropathic pain is a major cause of morbidity during the first two decades of life.[9] The clinical manifestations of Fabry disease affect patients' wellbeing, physical and social functioning, and ability to conduct activities of daily living, resulting in a decreased quality of life as compared with the general population.[9] Fabry disease may also present in adulthood with late-onset symptoms including hearing loss, proteinuria, left ventricular hypertrophy, arrhythmia, dyspnea, palpitations, and angina.[9] Chronic renal disease, cardiomyopathy, and cerebrovascular disease leading to renal failure, heart failure, or stroke are major complications of Fabry's disease.[9] Most males affected by Fabry disease die by the end of the sixth decade of life.[12]

Diagnosis of Fabry disease is frequently delayed by several years because of the non-specific nature of the presenting signs and symptoms.[9] Family history plays an important role in the evaluation of patients with possible Fabry disease.[11] Because Fabry disease is an X-linked genetic disorder and most cases result from inherited mutations rather than new mutations, most patients have blood relatives who are either affected males or carrier females.[12] Fabry disease can be reliably diagnosed in men by screening for greatly deficient or absent AGAL-A activity in plasma or peripheral leucocytes, or by genetic testing.[9] In women, screening for AGAL-A activity is unreliable because many heterozygous females have normal levels of AGAL-A.[12] Genetic testing is the only reliable means of confirming Fabry disease in women.[9] Deposition of incompletely metabolized glycosphingolipids, mainly Gb3, in multiple cell types is characteristic of Fabry disease.[17] Globotrysilceramide has been used as a biomarker in Fabry disease as measured in plasma and urine by tandem mass spectrometry.[17] The reference ranges for plasma and urinary Gb3 levels are 5.6 (3.6-7.5) µg/ml and 0.016 (0.01 - 0.03) mg/mmol of creatinine, respectively.[17] Globotrysilceramide levels are consistently elevated in most patients with classic Fabry disease. A summary of diagnostic criteria for Fabry disease is outlined in **Table 1.** Diagnosis of Fabry disease is likely in patients with 3 more points from the findings outlined in **Table 1**.

Table 1. Summary of diagnostic criteria for Fabry disease [18]

Criterion	Relevant Finding	Points toward diagnosis	Comment
Clinical features	Cornea verticillata or biopsy proven angiokeratomas	Presence of either or both of these will contribute 1 point	Need to exclude other causes
Alpha-galactosidase activity in plasma or leukocytes	Below 5%	1 point	Activity may not be reduced in females but low activity in a male member of the family cohort would contribute towards the diagnosis
Elevated plasma and/or urine biomarkers	Above reference range for lab; lyso-Gb3 is preferred	1 point	Conditions other than Fabry disease can elevate biomarkers
Molecular change	Mutation defined in literature as disease causing	1 point	High rate of error in annotation of mutations in available databases; the presence of a variant of uncertain significance should not be used to contribute towards the diagnosis
Pathologic findings	Presence of typical features of Fabry disease on biopsy of involved tissue	2 points in target organs (kidney, heart) 1 point in other organs (skin)	Should be interpreted by a pathologist with expertise in Fabry disease

Abbreviations: Gb3 = Globotrysilceramide

Prenatal diagnosis of Fabry disease can be accomplished by the assay of AGAL-A activity in chorionic villi obtained at 9 to 10 weeks of pregnancy or in cultured amniotic cells obtained by amniocentesis at approximately 15 weeks of pregnancy.[16] However, Fabry disease is not currently included in the United States Advisory Committee on Heritable Disorders in Newborns and Children Recommended Uniform Screening Panel.[19] Fabry disease newborn screening programs have been initiated in Missouri, Washington State, New York State, Pennsylvania, Illinois, New Jersey and New Mexico.[13] Newborn screening raises challenges in defining the most appropriate way to counsel families of infants diagnosed with Fabry disease, and how to effectively monitor and manage those infants in order to optimize clinical outcomes.

In the United States, 2 different Fabry disease treatments are available. The first medication, agalsidase beta (Fabrazyme®), was FDA-approved in 2003 and is administered via intravenous infusion every 2 weeks. Agalsidase beta supplies the deficient AGAL-A enzyme which catabolizes Gb3 in capillary endothelium of the kidney and other cell types.[20] A second therapy, oral migalastat (Galafold™), received FDA approval in 2018. Migalastat stabilizes specific mutant forms of AGAL-A. This increases enzyme trafficking to lysosomes and increases the probability that they mature to functional lysosomal enzymes that can catabolize glycosphingolipids.[21] Adjunctive treatment, including angiotensin converting enzyme inhibitors or angiotensin receptor blockers, antiplatelet drugs, and analgesics may also be initiated to manage other complications of Fabry disease. Studies have shown that therapies targeted towards replacing or enhancing the AGAL-A enzyme can delay but not always prevent some of the clinical complications of the disease.[1,3,7] Agalsidase and migalastat are not cures for Fabry disease and do not remove the need for concomitant medications or monitoring. It has been proposed that Gb3 levels may be considered as a biomarker of response to therapy with agalsidase or migalastat.[17] However, the reliability of Gb3 levels as a surrogate marker of treatment response for all patients has been questioned by investigators as some Fabry disease mutations do not respond to replacement therapy and many female heterozygotes with Fabry disease do not have elevated serum Gb3 levels.[22] More details about both therapies are presented in **Table 2** and discussed in more depth later in this report.

Table 2. FDA-Approved Therapies for Fabry disease[20,21]

Generic Drug Name (Brand)	Description	Indication	Availability/Route	Dose and Frequency	Approved Age for Administration
Agalsidase beta (Fabrazyme®)	Recombinant human a-galactosidase A enzyme with the same amino acid sequence as the native enzyme	Treatment of Fabry disease	5 mg and 35 mg vials for intravenous infusion after appropriate reconstitution and dilution	1 mg/kg intravenously every 2 weeks	≥8 years
Migalastat (Galafold™)	Pharmacological chaperone that reversibly binds to the active site of the alpha-galactosidase A protein which stabilizes the enzyme so it can catabolize lysosomal glycosphingolipids	Treatment of Fabry disease, with an amenable mutation	123 mg oral capsule	123 mg orally once every other day on an empty stomach	Adults (no specific age is referenced)

Abbreviations: gm = gram; kg = kilogram; mg=milligram

In the Oregon Health Plan, 36 patients had claims associated with Fabry disease within the past year. Of these 36 patients, 2 are enrolled in Fee-For-Service (FFS), 30 are enrolled in a Coordinated Care Organization (CCO), and 4 patients are no longer eligible. There have been no pharmacy claims for migalastat in the past 12 months in FFS or CCO populations. However, there were 7 physician administered drug (PAD) claims for agalsidase beta in the CCO population and 0 requests in the FFS population in the past year.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 5 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[17,23-27]

Guidelines:

United Kingdom Adult Fabry Disease Standard Operating Procedures

The U.K. standard operating procedures were prepared in 2012 by a group of prescribing physicians working in designated treatment centers at the invitation of the National Specialist Commissioning team.[4] The document is designed to regulate practice in England and is not a clinical guideline for use elsewhere.[4] At the time of publication, the only available treatments in the U.K. for Fabry disease were the 2 enzymes, agalsidase alpha (Replagal™) and agalsidase beta (Fabrazyme™). The advent of enzyme replacement therapy made it necessary to have explicit guidelines for the diagnosis, assessment, treatment and follow up of patients with Fabry disease and their families.[4]

Inclusion Criteria

1. In males with classic mutations (leukocyte enzyme activity <1%) enzyme replacement therapy should commence at diagnosis.
2. In females and those males with later onset mutations with higher levels of leukocyte enzyme activity enzyme replacement therapy should commence when one of the following criteria are fulfilled:

- Uncontrolled pain leading to a need to alter lifestyle or pain that interferes with quality of life.[4]
- Gastrointestinal symptoms such as pain, vomiting or altered bowel habit which are significantly reducing quality of life and not attributable to other pathology.[4]
- Clinically significant reduction in Glomerular Filtration Rate:
    A. < 80 ml/min adjusted according to age
    B. In males: proteinuria >300 mg/24 hours
    C. In males: microalbuminuria where a renal biopsy showed endothelial deposits, vascular or interstitial changes
    D. In children: persistent microalbuminuria (three consecutive early morning urine samples or 3 early morning urine samples over a period of one month).[4]
- Evidence of cardiac disease:
    A. EKG results:
        - Presence of left ventricular hypertrophy
        - Isolated repolarization abnormalities (in absence of other causes such as hypertension, aortic stenosis)
        - Conduction abnormalities: (Short PR interval, 1, 2 or 3 degree heart block, bundle branch block)
    B. Echocardiogram results:
        - Increased left ventricular mass (in patients with concentric remodeling or hypertrophy)
        - Increased left ventricular wall thickness (13 mm in any segment)
        - Left atrial enlargement
        - Valvular thickening/insufficiency
        - Systolic impairment (regional wall motion abnormality or reduction in left ventricular ejection fraction (< 50%)
        - Diastolic dysfunction (using age corrected Doppler assessment)
    C. Arrhythmia:
        - 24 hour EKG (or other documented EKG evidence) showing bradyarrhythmia, atrial arrhythmia, ventricular tachycardia.[4]
    D. Ischemic heart disease:
        - Positive exercise test, PET scan in the ABSENCE of angiographic ally significant epicardial coronary artery disease.[4]

- Cerebrovascular Disease:
    - Previous stroke or TIA in the absence of other risk factors
    - Progression of abnormal cerebral MRI scans[4]

Exclusion Criteria:
1. The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.[4]
2. Patients with Fabry disease who are deemed too severely affected to benefit from enzyme replacement therapy (e.g. severely incapacitated following stroke/ dementia).[4]
3. End stage renal failure requiring dialysis in the absence of other starting criteria.[4]
4. Severe cardiac fibrosis in the absence of other starting criteria.[4]

Efficacy Endpoints:
An improvement in or a prevention of deterioration in:
1. Renal function (defined by GFR or 24 hour urine creatine clearance or proteinuria)
2. Pain scores
3. Age appropriate Quality of Life measurement
4. Cardiac structure and function
5. Neurological status
6. Growth and development in children[4]

National Institute of Health and Care Excellence

National Institute of Health and Care Excellence (NICE) guidance for the use of migalastat in treating Fabry disease was published in 2017.[5] The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alpha and agalsidase beta) for treating Fabry disease.[5] The manufacturer submitted evidence from 2 randomized clinical trials (ATTRACT and FACETS) and 2 open-label extension studies.[5] ATTRACT was an 18-month open-label randomized controlled trial designed to show comparable effectiveness between migalastat and ERT.[5] The small sample size (n=60) in ATTRACT made a standard non-inferiority analysis impossible and the company presented its own pre-specified criteria for comparability.[5] FACETS was a 6-month double-blind randomized controlled trial, in which patients who had not had treatment before had either migalastat or placebo.[5] The trials reported biochemical outcomes of Gb3 and plasma lyso-Gb3 distributions and activity of the enzyme AGAL-A. These are primarily indicators of migalastat efficacy, but may not directly reflect patients' symptoms and do not themselves have a clear role in clinical decision making.[5] Intention-to-treat analyses were done based on all randomized patients in each trial. However, the ITT population included some patients who had mutations that were later found not to be amenable to migalastat.[5] This was because the assay used to determine the amenability of mutations was changed to conform to GLP laboratory standards; the updated assay is the one referred to in the marketing authorization for migalastat.[5] Therefore the company used modified ITT analyses which excluded these patients.[5]

The authors of the evidence review for NICE concluded the studies providing clinical effectiveness evidence for migalastat are limited and there are concerns about the design of both pivotal randomized controlled trials and the related open-label extension studies.[5] These concerns included:

- small populations and short trial durations
- imbalances in patient baseline characteristics between the trial arms in both randomized controlled trials and

- uncertainty as to how long individual patients had received migalastat because it was not reported how many patients were recruited to the open-label extension study from each arm of FACETS.[5]

Final NICE migalastat recommendations include:

1. Migalastat is recommended as an option for treating Fabry disease in people over 16 years of age* with an amenable mutation and only if enzyme replacement therapy (ERT) would otherwise be offered.[5] Criteria for starting and stopping ERT for Fabry disease are described in the United Kingdom Adult Fabry disease Standard Operating Procedures.[4]
2. The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alpha or agalsidase beta) for treating Fabry disease.[5]

*FDA approval for migalastat is for adults, a specific age range is not referenced.[21]

Canadian Agency for Drugs and Technologies in Health

A 2018 report from the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on the use of migalastat in treating Fabry disease.[6]
Migalastat is recommended for the long-term treatment of adults with a confirmed diagnosis of Fabry disease if the following criteria are met:

- For use in patients with an amenable mutation and who are otherwise eligible for enzyme replacement therapy for the treatment of Fabry disease.[6]
- Migalastat not to be used concomitantly with ERT.[6]
- Patients must be under the care of a clinician experienced in the diagnosis and management of Fabry disease.[6]

Due to the lack of large controlled studies in Fabry disease, most of the published guidelines regarding treatment are consensus based supported by data from observational trials and financially supported by manufacturer grants. For these reasons, 5 guidelines were excluded from this report.[28-31]

Randomized Controlled Trials:

A total of 128 citations were manually reviewed from the initial literature search. After further review, 128 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Drug Evaluation: Agalsidase beta (Fabrazyme®)

Agalsidase beta is a recombinant human AGAL-A enzyme approved for use in patients with Fabry disease to decrease Gb3 deposition in capillary endothelium of the kidney and other cell types.[20] Agalsidase beta is administered as an intravenous infusion once every 2 weeks at a dose of 1 mg/kg.[20] Agalsidase beta received accelerated FDA approval in 2003 due to its orphan drug status. The accelerated approval regulations provide that FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit.[2] Approval under these regulations requires that the applicant study the product further to verify and describe the clinical benefit.[2]

Efficacy

The first published trial evaluating the safety and efficacy of agalsidase beta was a randomized, double blind, placebo-controlled trial in 58 patients with Fabry disease.[1] Patients received either 1 mg/kg of agalsidase beta or placebo every two weeks for five months (20 weeks) for a total of 11 infusions. All patients were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion-associated reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion-associated reactions.[1] The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of Gb3 were cleared (reduced to normal or near-normal levels).[1] Microvascular deposits were graded

on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions).[1] After 20 weeks treatment with agalsidase beta resulted in clearance of Gb3 renal deposits in 20 of 29 (69%) treated patients compared with 0 patients in the placebo group (OR=0, p<0.001, CI not reported).[1] Patients in the agalsidase beta group also had decreased microvascular endothelial deposits of Gb3 in the skin (MD = 2.2, P<0.001, CI not reported) and heart (MD = 0.8, P<0.001, CI not reported) compared to placebo.[1] However, no differences between groups in symptoms or renal function were observed during the five-month trial.[1]

The FDA reviewers noted that accumulation of Gb3 within capillary endothelial cells is not a disease feature that is routinely assessed by physicians and validated for a relationship to clinically discernable consequences.[2] Thus, Gb3 accumulation does not constitute a clinically meaningful endpoint, and effects on intracellular Gb3 accumulation should not be regarded as substantial evidence of clinical efficacy.[2] In addition, the study was relatively short for a disorder where progression to renal failure may take many years.[2] It is also unknown which phase of the disease may be most amenable to demonstrating a clinical impact of treatment; so it is unknown if the most sensitive portion of the disease population was being studied in this first trial to evaluate the efficacy of agalsidase.[2]

Since agalsidase beta approval was based on data using a surrogate marker, the FDA required an additional trial to demonstrate clinical benefit.[2] The objective of the subsequent randomized, placebo-controlled trial was to evaluate the effect of agalsidase beta on disease progression in a composite analysis of renal, cerebrovascular, and cardiac events or death in patients with advanced Fabry disease and mild to moderate kidney disease (n=82).[3] Subjects were observed in the blinded portion of the study for 14 months and received open label treatment and follow-up for up to 35 months at 26 sites in 6 countries.[3] Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced composite clinical events including reduced renal function, cardiac events, stroke, or death.[3] In the composite assessment, agalsidase beta delayed the time to first clinical event compared to placebo (hazard ratio, 0.47; 95% CI, 0.21 to 1.03; P=0.06), but the results with not statistically signficant.[3] Individual assessments of each outcome (decreased renal function and incidence of cardiac and cerebrovascular events) were not significantly different between patients in agalsidase beta and placebo groups.[3]

Study limitations included a small sample size, only one third of the patients experienced clinical events, and some patients (n=6) withdrew before experiencing any event.[3] Eight patients had major protocol violations, including 5 patients who missed 22% to 87% of their infusions.[3] Nonsystematic errors introduced by protocol violations, such as missed treatments, could lead to bias toward treatment failure.[3] More information about both agalsidase beta studies is presented in **Table 5**.

A phase 4 post-marketing trial examined the clinical effects of agalsidase beta on the first occurrence of renal, cardiac or cerebrovascular events and serum creatinine over 10 years in 52 of the 58 patients included in the first RCT that evaluated agalsidase beta.[19] Severe clinical events were defined as chronic dialysis, kidney transplant, myocardial infarction, congestive heart failure, major cardiac procedures (i.e., implantation of a balloon pump, cardioverter-defibrillator or first pacemaker; or bypass surgery), stroke and death.[19] Eighty-one percent of patients (42/52) did not experience any severe clinical event during the treatment interval and 94% (49/52) were alive at the end of the study period.[19] Ten patients reported a total of 16 events.[19] The most frequent clinical event was stroke; five patients (9.6%) had a total of eight strokes.[19] Four patients (7.7%), all with high renal involvement at baseline, had a severe renal event.[19] Two cardiac events were reported; cardiac-related death at age 52 years and myocardial infarction at age 53.[19] Two patients with multiple strokes were in their 20's at the time of their first severe clinical event.[19] Renal and cardiovascular events occurred most frequently in patients older than 40 years of age.[19]

Safety

In clinical trials with agalsidase beta, approximately 50 to 55% of patients experienced infusion reactions during drug administration. The majority of infusion reactions were related to febrile reactions or pain symptoms. Most patients in clinical trials were pretreated with acetaminophen. According to the manufacturer, pretreatment with an antipyretic and antihistamine is recommended in patients experiencing infusion associated reactions.[20] A summary of common adverse reactions that occurred with agalsidase beta compared to placebo in clinical trials is presented in **Table 2.**

Table 3. Adverse Reactions Observed with Agalsidase Beta During Clinical Trials.[20]

Adverse Reaction	Agalsidase beta (n=80)	Placebo (n=60)
Upper respiratory infection	44%	30%
Chills	43%	12%
Pyrexia	39%	22%
Headache	39%	28%
Cough	33%	25%
Paresthesia	31%	18%
Fatigue	24%	17%
Peripheral Edema	21%	7%
Dizziness	21%	8%
Rash	20%	10%
Pain in Extremity	19%	8%
Nasal Congestion	19%	15%
Myalgia	14%	5%
Hypertension	14%	5%
Pruritus	10%	3%
Tachycardia	9%	3%
Burning Sensation	6%	0%
Anxiety	6%	3%
Depression	6%	2%
Wheezing	6%	0%
Hot Flush	5%	0%

Ninety-five of 121 (79%) of adult patients and 11 of 16 (69%) pediatric patients treated with agalsidase beta in clinical studies developed IgG antibodies to agalsidase beta.[20] Most patients who develop IgG antibodies do so within the first three months of exposure.[20] IgG seroconversion in pediatric patients was associated with prolonged half-life of agalsidase beta, a phenomenon rarely observed in adult patients.[20] Assessment of inhibition of enzyme uptake in cells has not been performed.[20] No general pattern was seen in individual patient reactivity over time.[20] The clinical significance of binding and/or inhibitory antibodies to agalsidase beta is not known with respect to efficacy of treatment or inhibition of enzyme activity.[20]

Look-alike / Sound-alike Error Risk Potential: No results reported.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved renal function
2) Improved cardiac symptoms
3) Improved cerebrovascular symptoms
3) Mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clearance of Gb3 renal deposits (surrogate endpoint)
2) Delay in progression of renal, cerebrovascular, and cardiac events

Table 4. Pharmacology and Pharmacokinetic Properties of Agalsidase[20]

Parameter	
Mechanism of Action	Agalsidase beta provides an exogenous source of alpha-galactosidase A in Fabry disease patients.
Oral Bioavailability	N/A – administered via intravenous route
Distribution and Protein Binding	Volume of distribution: 81-570 mL/kg
Elimination	N/A
Half-Life	45 to 102 minutes
Metabolism	Specific pathways are unknown

Abbreviations: N/A = not available

Table 5. Comparative Evidence Table for Agalsidase Beta

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Eng CM, et al.[1] MC, DB,PC N=58	1. Agalsidase beta 1 mg/kg IV every other week x 20 weeks 2. Placebo IV every other week x 20 weeks Followed by OL extension study for 6 additional months	Demographics: 1. Mean age: 28-32 yrs 2. Male: 97% 3. Race: White-92% Key Inclusion Criteria: 1. At least 16 years old 2. Subjects had enzymatically confirmed diagnosis of Fabry's disease 3. Subjects had a plasma level AGAL-A of < 1.5 nmol per/hr/mL OR < 4 nmol/hr/kg in leukocytes	ITT: 1.29 2.29 Attrition: 1. 0 2. 0	Primary Endpoint: Percentage of patients with reduced renal microvascular Gb3 deposits at 20 weeks 1. 20 (69%) 2. 0 (0%) OR = 0; P<0.001 Secondary Endpoints: Mean change in Gb3 deposits in myocardium specimen 1. -0.6 ± 0.7 2. 0.2 ± 0.8 P<0.001; 95% CI NR	 NA NA	Rigors 1. 14 (48%) 2. 0 (0%) P=0.004 Fever 1. 7 (24%) 2. 1 (3%) P=0.024 Headache 1. 5 (17%) 2. 2 (7%) P value NR	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Baseline characteristics similar in both arms. Performance Bias: Unclear. Initial 20 weeks were double blinded, but method of blinding not stated. Detection Bias: Unclear. Pathologists who examined biopsy results were blinded to treatment arm. Methods for blinding not described. Attrition Bias: Low. No patients withdrew from the trial. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Supported by NIH grant. Primary authors received grant support from Genzyme.

		Key Exclusion Criteria: 1. Scr > 2.2 mg/dl 2. Undergoing dialysis 3. Kidney transplant recipient		Mean change in Gb3 deposits in skin specimen 1. -2.1 ± 0.7 2. -0.1 ± 1.0 P<0.001; 95% CI NR Mean change in Gb3 deposits in kidney specimen 1. -1.6 ± 1.2 2. -0.1 ± 1.1 P<0.001; 95% CI NR	NA NA	Chills 1. 4 (14%) 2. 0 P value NR Hypertension 1. 3 (10%) 2. 0 (0%) P value NR Percentage of overall AEs, SAE & withdrawals due to AE NR	NA NA	**Applicability**: Patient: Applies to patients with confirmed Fabry disease diagnosis aged 16 yrs and older with normal renal function. Intervention: Agalsidase dosing evaluated in Phase 1 and 2 trials. Comparator: Placebo x 20 weeks followed by OL arm. Outcomes: Surrogate endpoint: Gb3 tissue concentrations from kidney, skin, and heart biopsies. Setting: 8 study sites: United States: 3 The Netherlands: 1 United Kingdom: 2 France: 2
2. Banikazemi M, et al.[3] DB, PC, MC, RCT N = 82	1. Agalsidase beta 1 mg/kg IV every other week x 35 months 2. Placebo IV every other week x 35 months	Demographics: 1. Mean age: 44 to 46 yrs 2. Male: 87.5% 3. Race: White -87.5% 4. Mean GFR = 53 mL/min Key Inclusion Criteria: 1. At least 16 years old 2. Subjects had enzymatically confirmed diagnosis of Fabry's disease 3. Subjects had a plasma level AGAL-A of < 1.5 nmol per/hr/ml OR AGAL-A < 4 nmol/hr/kg in leukocytes 4. Scr ≥1.2 mg/dL and < 3.0 mg/dL Key Exclusion Criteria: 1. Undergoing dialysis 2. Kidney transplant recipient 3. Patients with history of stroke, unstable angina, or myocardial infarction within 3 months of trial entry	ITT: 1. 51 2. 31 PP: 1. 43 2. 28 Attrition 1. 8 (16%) 2. 3 (10%)	Primary Endpoint: Proportion of patients with a clinical event (renal, cardiac, CVA, or death) 1. 14 (27%) 2. 13 (42%) HR = 0.47 (95% CI 0.21 to 1.03); P=0.06 Secondary Endpoints: Renal events (33% increase in serum creatinine level) 1. 10 (20%) 2. 7 (23%) HR=0.49 (95% CI 0.17 to 1.4); P=0.18 Cardiac events (arrhythmia, angina, MI) 1. 3 (6%) 2. 4 (13%) HR=0.42 (95% CI 0.058 to 2.7); P=0.42 Cerebrovascular events (stroke, TIA) 1. 0 (0%) 2. 2 (7%) HR=0 (95% CI 0 to 3.2); P=0.14 Death 1. 2 (2%) 2. 1 (0%) HR NR	 NS NS NS NA	1. Treatment-related AEs 1. 31 (61%) 2. 10 (32%) 2. SAEs 1. 18 (35%) 2. 10 (32%) 3. AEs resulting in treatment termination 1. 4 (8%) 2. 1 (3%) P values and 95% CI NR for all	 NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 2:1 treatment to placebo via computer generated program in block size of 3. Additional details about randomization strategy were not available for review. Baseline characteristics were balanced. Performance Bias: Low. Sponsor staff, investigators, and patients were blinded to treatment allocation using identical packaging. Detection Bias: Low. Agalsidase and placebo were packaged identically. Attrition Bias: Low. 2 subjects died, 3 withdrew consent, and 3 withdrew per protocol in active comparator arm. In placebo arm, 1 subject died and 2 subjects withdrew consent. Reporting Bias: Unclear. Protocol unavailable Other Bias: Unclear. Genzyme personnel were involved in the trial design, data management, and statistical analyses. **Applicability**: Patient: Fabry disease in patients over 16 yrs with mild to moderate renal impairment. Most patients were between 18 and 65 yo. Intervention: Agalsidase beta dose evaluated in Phase 1 and Phase 2 trials. Comparator: Placebo Outcomes: Composite endpoint of clinical events (renal, cardiac, cerebrovascular and death). Setting: 26 referral centers in 6 countries in Europe and North America

Abbreviations [alphabetical order]: AE = adverse events; AGAL-A = alpha-galactosidase A; ARR = absolute risk reduction; CI = confidence interval; CVA = cerebrovascular accident; DB = double blind; dL = deciliter; Gb3 = globotriaosylceramide; GFR = glomerular filtration rate; hr = hour; HR = hazard ratio; ITT = intention to treat; IV = intravenous; kg = kilograms; MC = multicenter; MI = myocardial infarction; mL = milliliters; N = number of subjects; NA = not applicable; nmol= nanomole; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open label; OR = odds ratio; PC = placebo control; PP = per protocol; RCT = randomized clinical trial; SAE = serious adverse events; Scr = serum creatinine; TIA = transient ischemic attack; yo = years old; yrs = years

New Drug Evaluation: Migalastat (Galafold™)

The FDA granted accelerated approval of migalastat (Galafold™) in August 2018. Migalastat is an oral medicine for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene variant based on in vitro assay data.[21] The definition of an amenable mutation is one that increases activity of alpha galactosidase A in an in vitro cell culture system (human embryonic kidney [HEK] cells) by 1.2 times the baseline activity with an absolute value for enzyme activity of 3% or greater when compared with wild type values.[32] Migalastat is a pharmacological chaperone designed to bind selectively and reversibly to the active site of the enzyme AGAL-A.[8] This binding stabilizes AGAL-A in the endoplasmic reticulum facilitating its proper trafficking into lysosomes.[8] When in lysosomes, in an acidic pH and in a higher relative concentration of the relevant substrates, migalastat dissociates from AGAL-A, thereby allowing it to catalyze the breakdown of Gb3 and globotriaosylsphingosine (lyso-Gb3).[8] The accelerated approval was based on the surrogate endpoint of reduction in kidney interstitial capillary cell Gb3 substrate after 6 months of therapy.[21] As a condition of accelerated approval, the manufacturer will continue to study migalastat in a confirmatory Phase 4 program.[21] Migalastat is available as a 123 mg capsule and is dosed as 1 capsule every other day on an empty stomach.

Efficacy

The FDA approval of migalastat was based on data from a phase 3 study in 67 treatment-naïve patients with Fabry disease (FACETS).[7] Subjects were randomized in a 1:1 ratio to receive either migalastat 150 mg or a placebo every other day for the first 6 months of the study.[7] In the second 6 months, all patients were treated with open-label migalastat. The trial enrolled patients who had a "responsive" GLA variant using an in vitro assay, the CT HEK-293 assay.[7] As the CT HEK293 assay underwent validation in parallel with the phase 3 trial, 17 of the 67 enrolled patients were determined to have nonamenable GLA variants using the validated HEK assay.[7] Consequently, the final efficacy population was reduced from 67 to 50 patients.[7] Furthermore, among these 50 patients, only 45 had available histology data both at baseline and at month 6. The final population used for the analysis of efficacy consisted of 45 patients with amenable GLA variants and available histology data, of whom 29 were females and 16 were males.[7]

The primary efficacy outcome was a surrogate endpoint, the proportion of patients with 50% or greater reduction in the average number of GL-3 inclusions per kidney interstitial capillary (KIC) in biopsy samples. Both the ITT and the modified ITT (patients with amenable GLA variants and available histology) populations were assessed from baseline to month 6.[7] In the ITT population, which included 17 patients with non-amenable GLA variants, the primary efficacy outcome did not show a significant treatment effect, as a response was achieved in 13 of 34 (38%) migalastat-treated patients compared to 9 of 33 (27%) placebo-treated patients (p = 0.3, CI not reported).[7] In the modified ITT population with available histology data 13 of 25 (52%) patients on migalastat achieved the primary efficacy outcome compared to 9 of 20 (45%) patients on placebo (statistical data not reported).[7] Among the 29 females with amenable GLA variants, 8 of 18 (44%) in the migalastat group achieved the primary efficacy outcome versus 5 of 11 (45%) in the placebo group (statistical data not reported).[7] In contrast, among the 16 males with amenable GLA variants, 5 of 7 (71%) in the migalastat group achieved the primary efficacy outcome as compared to 4 of 9 (44%) in the placebo group (statistical data not reported).[7]

This clinical trial involved a small numbers of subjects with very mild disease manifestations and did not include patients with high levels of proteinuria which is a known risk factor for adverse cardiovascular and renal events in Fabry disease.[8] The trial was also of short duration. In addition, baseline imbalances in patient

characteristics were observed between the 2 groups. Notably, placebo patients had a two-fold higher baseline urine GL-3 concentration than migalastat patients, which is of unclear clinical significance as GL-3 concentration in urine cannot reliably be correlated with disease severity in Fabry disease.[8] In addition, at baseline, there was a large difference between males and females in terms of GL-3 inclusion burden.[8] Males started with a higher baseline GL-3 inclusion burden as compared to the females, which is indicative of more extensive substrate deposition in KIC and, thus, more severe disease on a histologic level.[8] There was also a higher amount of proteinuria in the placebo patients than in the migalastat patients, which may explain why more patients in the placebo group were treated with an ACE inhibitor or ARB during the trial.[8] Of note, baseline renal function (as measured by eGFR) was similar in both groups.[8] Published data are not yet available on the effects of migalastat in patients with more advanced disease or with duration of therapy beyond 2 years.[8]

Safety

During the phase 3 trial, there were no deaths or serious adverse events attributed to migalastat treatment.[21] The most frequently reported adverse events in patients treated with migalastat in the FACETS trial over the first 6 months (and with a higher incidence than placebo) included headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia.[7] Incidence of adverse effects compared to placebo is presented in **Table 6.** No clinically significant laboratory or vital sign changes were observed in migalastat-treated patients in the phase 3 trial.[21] Migalastat showed no effects on the QT interval and electrocardiograms performed during the phase 3 trial revealed no clinically significant changes from baseline during migalastat treatment.[21] Migalastat is not recommended in patients with severe renal impairment (eGFR < 30 mL/min/1.73m2).[21] No dosage adjustment in patients with mild or moderate renal impairment is recommended.[21]

Table 6. Adverse reactions reported with migalastat during the first 6 months of treatment[21]

Adverse Reaction	Migalastat (n=34)	Placebo (n=33)
Headache	35%	21%
Nasopharyngitis	18%	6%
Urinary tract infection	15%	0%
Nausea	12%	6%
Pyrexia	12%	3%
Abdominal pain	9%	3%
Back pain	9%	0%
Diarrhea	95	3%
Epistaxis	9%	3%

Look-alike / Sound-alike Error Risk Potential: Miglustat (Zavesca®) used to treat Gaucher disease

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved renal function
2) Improved cardiac symptoms
3) Improved cerebrovascular symptoms
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of ITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months (surrogate endpoint)

Table 7. Pharmacology and Pharmacokinetic Properties of Migalstat[21]

Parameter	
Mechanism of Action	Pharmacologic chaperone designed to bind selectively and reversibly to the active site of AGAL-A enzyme which allows breakdown of Gb3
Oral Bioavailability	75%, food decreases absorption by 37 to 42%
Distribution and Protein Binding	Volume of distribution = 89 L, no protein binding detected
Elimination	Renal: 77% of dose
Half-Life	4 hours
Metabolism	Substrate of UDPGT

Abbreviations: AGAL-A = alpha-galactosidase A; Gb3 = globotriaosylceramide

Table 8. Comparative Evidence Table for Migalastat

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Germain DP, et al.[7] Phase 3 RCT, DB, PC, MC 6 months	1. Migalastat 150 mg orally every other day 2. Oral placebo every other day Initial 6 month DB stage (Stage 1) followed by 6 month OL phase (Stage 2) where all patients received migalastat	Demographics: 1. Mean age: 42 yo 2. Gender: Female 64% 3. Years since diagnosis: 6.3 4.ACE/ARB use: 42% 5.Prior ERT use: 22% 6.Suitable *GLA* mutation: 75% 7.Race: White 93% Key Inclusion Criteria: 1. Aged 16 to 74 yo with Fabry disease with mutation responsive to migalastat 2. No ERT treatment for 6 months before enrollment 3. GFR > 30 mL/min/1.73 m^2 4. If taking ACE/ARB must be on a stable dose for 4 weeks prior to study inclusion 5. Urine Gb3 concentration ≥ 4 times the ULN Key Exclusion Criteria: 1. Subject has undergone kidney transplantation or is undergoing dialysis 2. GFR < 30 mL/min 3.QTC ≥ 450 msec for males or ≥ 470 msec for females	ITT: 1. 34 2. 33 mITT (responsive mutation with histology data): 1. 25 2. 20 ITT Attrition: 1. 0 (0%) 2. 3 (9%)	Primary Endpoint: Percentage of ITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months 1. 13 (38%) 2. 9 (27%) P=0.30; 95% CI NR Secondary Endpoints: Percentage of mITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months 1. 13 (52%) 2. 9 (45%) P=0.55; 95% CI NR Median change in Gb3 inclusions in kidney interstitial capillary from baseline at 6 months in ITT population 1. -40.8% 2. -5.6% P=0.10; 95% CI NR Mean change in Gb3 inclusions in kidney interstitial capillary from baseline at 6 months in mITT population 1. -0.25 2. 0.07 P=0.008; 95% CI NR	NS NS NS NA	Serious AE during first 6 months 1. 5 (15%) 2. 2 (6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 1:1 to each arm and stratified by gender using a central randomization system. Concurrent validation of migalastat-amenable mutation assay conducted during DB phase. 17 patients subsequently excluded due to mutation unresponsive to therapy. Baseline characteristics imbalanced. Performance Bias: Low. Placebo matched to active comparator in capsules similar in appearance and size. All subjects instructed to take medication on an empty stomach. Detection Bias: Low. All subjects, investigators, and sponsors blinded to treatment arm. Attrition Bias: Low. 3 subjects withdrew from the placebo arm in the first 6 mos due to pregnancy (1) and withdrawal of consent (2). Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Funded by Amicus Therapeutics. Data collection and analyses included authors and manufacturer. Over 50% of authors report grants or other funding from the manufacturer. **Applicability**: Patient: Study conducted in males and females with Fabry disease and with a GLA mutation responsive to migalastat. Patients with severe renal impairment were excluded from the trial. Majority of enrolled patients were female. Intervention: Migalastat 150 mg dose evaluated in Phase 2 trials. FDA approved dose is 123 mg. Comparator: Placebo controlled trial Outcomes: Surrogate endpoint with unclear link to clinical outcomes Setting: International settings including 30 sites

Abbreviations [alphabetical order]: ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; GFR = glomerular filtration rate; ITT = intention to treat; MC = multicenter; mITT = modified; mL= milliliters; min = minute; intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; OL = open-label; PC= placebo controlled; PP = per protocol; ULN = upper limit of normal; yo = years old

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FABRAZYME safely and effectively. See full prescribing information for FABRAZYME.

FABRAZYME (agalsidase beta) for injection, for intravenous use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.1)
- Administer antipyretics prior to infusion. (2.1)
- See the full prescribing information for the recommended infusion rate. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion-associated reactions. (5.1)
- Infusion-associated reactions occurred in 59% of patients during Fabrazyme administration in clinical trials. Some reactions were severe. In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. (5.2)
- If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen as clinically indicated. (5.2)
- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions, and these patients should be monitored closely during Fabrazyme administration. (5.3)
- Readministration of Fabrazyme to patients who have previously experienced severe or serious allergic reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel and with appropriate medical support measures readily available. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20% and >2.5% compared to placebo) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GALAFOLD safely and effectively. See full prescribing information for GALAFOLD.

GALAFOLD™ (migalastat) capsules, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

GALAFOLD™ is an alpha-galactosidase A (alpha-Gal A) pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data. (1, 12.1)

This indication is approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

----------DOSAGE AND ADMINISTRATION----------

- Select adults with confirmed Fabry disease who have an amenable *GLA* variant for treatment with GALAFOLD.
- Treatment is indicated for patients with an amenable *GLA* variant that is interpreted by a clinical genetics professional as causing Fabry disease (pathogenic, likely pathogenic) in the clinical context of the patient. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable *GLA* variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease). (2, 12.1)
- The recommended dosage regimen of GALAFOLD is 123 mg orally once every other day at the same time of day. (2)
- Take on an empty stomach. Do not consume food at least 2 hours before and 2 hours after taking GALAFOLD to give a minimum 4 hours fast. (2)
- Do not take GALAFOLD on 2 consecutive days. (2)
- If a dose is missed entirely for the day, take the missed dose only if it is within 12 hours of the normal time that the dose should have been taken. If more than 12 hours have passed, resume taking GALAFOLD at the next planned dosing day and time and according to the every-other-day dosing schedule. (2)
- Swallow capsules whole; do not cut, crush, or chew. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 123 mg migalastat. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------ADVERSE REACTIONS----------

Most common adverse drug reactions ≥ 10% are: headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amicus Therapeutics at 1-877-4AMICUS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2018

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to June 25, 2019

1. Fabry Disease	*2306*
2. alpha-Galactosidase	*1834*
3. Migalastat.mp	*94*
4. 2 or 3	*1888*
5. 1 and 4	*1148*

6. limit 5 to (english language and humans and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) 128

Fabry Disease

Goal(s):

- Ensure medically appropriate use of drugs for Fabry Disease

Length of Authorization:

Up to 12 months

Requires PA:

- Agalsidase beta and migalastat

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the provider a specialist in managing Fabry disease?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for migalastat?	**Yes:** Go to # 7	**No:** Go to # 10
7. Does the patient have a mutation that is amenable to migalastat therapy as confirmed by a genetic specialist?	**Yes**: Got to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently receiving agalsidase beta?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 9
9. Is the patient 18 years of age or older?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. Migalastat is only FDA-approved for use in adults.
10. Is the patient a male with diagnosis of Fabry disease confirmed by genetic testing or deficiency in alpha-galactosidase A enzyme activity in plasma or leukocytes?	**Yes:** Go to # 11	**No:** Go to # 12
11. Does the patient have end stage renal disease requiring dialysis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
12. Is the patient a female and a documented Fabry disease carrier confirmed by genetic testing with significant clinical manifestations of Fabry disease such as: • Uncontrolled pain that interferes with quality of life • Gastrointestinal symptoms that are significantly reducing quality of life and not attributable to other pathology • Mild to moderate renal impairment (GFR > 30 mL/min) • Cardiac disease (left ventricular hypertrophy, conduction abnormalities, ejection fraction< 50%, arrhythmias) • Previous stroke or TIA with retained neurologic function	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement in one of the following: • Renal function • Pain Scores • Quality of Life measurement • Cardiac function • Neurologic status • Growth and development in children	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 3/19 (DM)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: Aemcolo™ (rifamycin) delayed release tablet, oral

Date of Review: September 2019
Generic Name: rifamycin

End Date of Literature Search: December 2018
Brand Name (Manufacturer): Aemcolo™ (Cosmo Technologies, Ltd)
Dossier Received: no

Research Questions:

1. What is the efficacy of rifamycin compared to placebo or currently available therapy for the treatment of adults with travelers' diarrhea (TD)?
2. Is rifamycin safer than alternative treatments for TD?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with rifamycin?

Conclusions:

- Low strength of evidence from one poor quality randomized controlled trial (RCT) demonstrated that rifamycin is more effective compared to placebo in reducing the duration of TD caused by *E.Coli* (46 hours vs. 68 hours; p=0.0008).[1] In addition, low strength of evidence shows that a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%; difference=24.5%; p=0.0001; 95% Confidence Interval (CI) 11.3 to 37.7; Number Needed to Treat (NNT) 5).[1] Clinical cure was defined by the investigators as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1]
- A non-inferiority study at high risk of bias provides insufficient evidence that rifamycin was non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] In this trial investigators reported the median time to last unformed stool (TLUS) in Per Protocol (PP) analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035 for non-inferiority).[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2]
- There is low-quality evidence that the tolerability of rifamycin is comparable to placebo or ciprofloxacin. In the 2 low quality studies, constipation (3.5% rifamycin, 1.5% placebo) and headache (3.3% rifamycin, 1.9% ciprofloxacin) were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater than placebo or ciprofloxacin.[3] No severe adverse effects were reported during either RCT. Only 1% (n=6) of patients from both trials were reported to have discontinued the trials due to an adverse effect.[1,2]
- The safety of rifamycin has not been evaluated in pediatric patients, pregnant women, breast feeding women, or adults aged 65 years and older.
- The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than *E.coli* or TD complicated by fever and bloody diarrhea. The safety of rifamycin has not been evaluated in pediatric patients.
- Evidence is insufficient to determine the comparative safety of rifamycin and rifaximin or azithromycin.

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- Designate rifamycin as non-preferred on the preferred drug list (PDL).
- Add rifamycin to PA criteria for rifaximin to ensure appropriate utilization of both medications. (**Appendix 2**).

Summary of Prior Reviews and Current Policy

Previous P and T Committee recommendations for drugs used to manage infectious diarrhea were addressed at the May 2015 meeting when PA criteria for the use of rifaximin in hepatic encephalopathy (HE) were presented. Use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. Rifaximin also has an FDA-approved indication for treatment of traveler's diarrhea caused by noninvasive strains of Escherichia coli. Both HE and infectious diarrhea are funded conditions under the OHP.

Background:

Travelers' diarrhea is defined as passage of 3 or more unformed stools plus at least 1 accompanying symptom in a 24 hour period that develops during or within 14 days of returning from travel to a resource-limited location.[4] Travelers' diarrhea is the most common illness afflicting travelers, and several observational studies report an incidence of 10-40% after a 2-week travel period depending on destination and traveler characteristics.[5] As a large number of individuals experiencing symptoms self-treat, the actual magnitude of the disease burden is uncertain.[3] Travel destination has a major impact on the risk for TD. According to the Centers for Disease Control and Prevention (CDC), the world is divided into 3 grades of TD risk: low, intermediate and high.[4]

- Low-risk countries include the United States, Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe.[4]
- Intermediate-risk countries include those in Eastern Europe, South Africa, and some Caribbean islands.[4]
- High-risk areas include most of Asia, the Middle East, Africa, Mexico, and Central and South America.[4]

Travelers' diarrhea is usually infectious and is caused by microbial pathogens endemic at the travel destination.[6] Most TD cases are contracted from contaminated food and less commonly from water.[1] Bacteria account for up to 90% of identified infectious etiologies for acute TD, predominately enterotoxigenic *E. coli* (ETEC), and enteroaggregative *E. coli* (EAEC), although there is regional variability.[7] Other bacterial pathogens that can cause TD include *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species.[8] There is increasing recognition of *Aeromonas* species, *Plesiomonas* species, and newly identified pathogens (*Acrobacter, Larobacter*, enterotoxigenic *Bacteroides fragilis*) as potential causes of TD as well.[4] Regardless of cause, most cases of TD have a similar clinical appearance, with patients complaining of watery diarrhea with abdominal pain or cramps of variable severity.[8] The disease is present if travelers develop at their destination 3 or more unformed stools per 24 hours plus at least 1 additional symptom, such as abdominal cramps, tenesmus, nausea, vomiting, fever, or fecal urgency.[5] Travelers are recognized as an important vector for transmission of emerging and multi-drug resistant (MDR) enteropathogens globally.[9]

Rates of TD can be reduced if travelers are educated how to select safe food and beverages items.[8] Safe foods include those served steaming hot (≥ 59°C), dry items such as bread, and fruit that can be peeled.[8] Travelers should remember to use only beverages that are sealed, treated with chlorine, boiled, or are otherwise known to be purified.[4] When otherwise healthy travelers develop diarrhea they should be encouraged to consume fluids and salty foods.[8] Bismuth subsalicylate has antibacterial properties and prevents 65% of expected TD cases when taken at recommended doses (2.1 gm per day divided into 4 doses).[8] Probiotics are not recommended due insufficient evidence demonstrating their efficacy.[4] Antimotility agents provide symptomatic relief and are useful therapy in TD.[4] Loperamide or diphenoxylate can reduce frequency of bowel movements and therefore enable travelers to ride on public transportation.[4] Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.[4] Loperamide can be used in children, and liquid formulations are available.[4]

Antimicrobial therapy is not routinely recommended for mild TD, but should be considered for people with suspected *Shigella* or *Campylobacter* species and certain *E. coli* infections and moderate to severe TD symptoms.[8] Knowledge of global resistance patterns can help inform the choice of empiric antibiotics in returning travelers.[10] Increasing microbial resistance to the fluoroquinolones, especially among *Campylobacter* isolates, may limit their usefulness in many destinations, particularly South and Southeast Asia, where both *Campylobacter* infection and fluoroquinolone resistance is prevalent.[4] Increasing fluoroquinolone resistance has been reported from other destinations and in other bacterial pathogens, including in *Shigella* and *Salmonella*.[4] In general, azithromycin or a fluoroquinolone are recommended.[5] In particular, azithromycin is the preferred option for patients with fever or dysentery (bloody or mucoid diarrhea), pregnant women, children, and for travelers to locations (such as Southeast Asia) where fluoroquinolone-resistant pathogens are prevalent.[5] Fluoroquinolones had long been the first choice for treatment of travelers' diarrhea, but the emergence of resistance to this drug class and increased awareness of adverse events make the risk-benefit assessment less clear.[5] Rifaximin is an alternative for travelers' diarrhea suspected to be caused by noninvasive strains of *E. coli*, but its effectiveness against invasive pathogens is unknown, and it should not be used in patients with fever or bloody diarrhea.[5] Due to widespread resistance, sulfamethoxazole/trimethoprim is no longer recommended to treat TD.[3] A 2000 Cochrane review concluded that antibiotics shorten the overall duration of moderate to severe traveler's diarrhea to about a day and a half.[11] The mean duration of travelers' diarrhea, even if untreated, is 4 to 5 days.[12]

Guidelines:

American College of Gastroenterology

In 2016, the American College of Gastroenterology (ACG) published a clinical guideline focused on diagnosis, treatment, and prevention of acute diarrheal infections in adults.[13] No financial support was received by any of the authors for development of the recommendations. Potential conflicts of interest due to research support or participation on advisory boards was clearly stated in the publication. All 3 primary authors serve on the advisory boards of several pharmaceutical manufacturers including the manufacturer of rifaximin. One of the authors is an employee of the U.S. government and completed this work as part of his official duties. The evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[14] Treatment recommendations based on moderate to high quality evidence are highlighted below. **Table 1** includes a summary of antibiotics recommended by the ACG to treat acute diarrhea symptoms in adults.

- The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of TD where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics (Strong recommendation, high level of evidence).[13]
- Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild to moderate illness (Strong recommendation, high level of evidence).[13]
- In patients receiving antibiotics for TD, adjunctive loperamide therapy can be administered to decrease duration of diarrhea and increase chance for a cure (Strong recommendation, moderate level of evidence).[13]

Table 1. Acute diarrhea treatment recommendations for adults[13]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally **OR**	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course

	500 mg once a day	3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant ETEC are suspected.
b. Preferred regimen for dysentery or febrile diarrhea.
c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Rifamycin, an antibiotic closely related to rifaximin, binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription.[15] This results in inhibition of bacterial synthesis and growth. The FDA approved indication for rifamycin is treatment of TD caused by non-invasive species of *E.Coli* in adults.[15] Rifamycin is poorly absorbed into the systemic circulation after oral administration.[15] It is manufactured with an enteric coating which allows the delivery of the active ingredient to the distal small bowel and colon.[15] Administration of rifamycin directly to the colonic lumen minimizes activity on the beneficial flora of the upper intestinal tract.[15] The Food and Drug Administration (FDA) approval of rifamycin was based on data from two randomized, multi-center, controlled Phase 3 clinical trials which were conducted entirely outside of American research sites. Trial 1 (NCT01142089), a placebo-controlled superiority study, was conducted at sites in Guatemala and Mexico. This trial was the primary basis for assessment of efficacy by the FDA.[3] The data from Trial 2 (NCT01208922), a non-inferiority comparison of rifamycin to ciprofloxacin, was considered supportive for efficacy in the FDA review.[3] Trial 2 was conducted at clinical sites in India, Guatemala and Ecuador.[2] This trial was funded by a different manufacturer than Trial 1 and was not conducted under an American Investigational New Drug (IND) application.[3]

Trial 1 enrolled 264 adults traveling to Mexico or Guatemala experiencing acute diarrhea.[1] Subjects were randomized 3:1 to rifamycin (400 mg orally twice daily for 3 days) or placebo. Patients with fever and/or bloody stools were excluded from the trial. Patients recorded in diaries the date, time, and consistency of stools (formed, soft, or watery), study drug administration, symptoms of enteric infection, and adverse events.[1] Safety and efficacy were assessed at visit 2 (day 2), visit 3 (day 4 or 5), and visit 4 (days 6–10).[1] Drug compliance was verified by review of diaries and by counting remaining tablets when medicine containers were returned.[1] Stool samples were collected at visit 1 and visit 3 and sent to a central laboratory (Center for Infectious Diseases at University of Texas School of Public Health) for pathogen identification and antibiotic susceptibility testing.[1] Patients were eligible to receive rescue therapy if diarrhea and/or symptoms of enteric infection worsened or failed to improve. Patients receiving rescue therapy were withdrawn from the study and given the maximum TLUS (time to last unformed stool) value of 120 hours.[1] The most common reason for not completing the trial was that the patient required rescue medication, seen in 12.3% of placebo patients and 8.5% of rifamycin patients.[1]

The primary endpoint was the length of time between administration of the first medication dose to last unformed (watery or soft) stool (TLUS) before achieving clinical cure.[1] Clinical cure was defined as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1] The investigators reported TLUS was significantly shorter in the rifamycin group (median: 46.0 hours) compared with placebo (median: 68.0 hours; p=0.0008, due to the distribution of placebo TLUS values, it was not possible to compute a 95% confidence interval for this difference).[1] In addition, a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%) [Difference=24.5%; p=0.0001; 95% CI 11.3 to 37.7; NNT 5].[1] The predominant pathogen identified from collected stool samples was *E. coli*.[1]

Trial 2 was a randomized, double-blind, multi-center, non-inferiority trial in which subjects were randomized 1:1 to a 3-day course of rifamycin (400 mg orally twice daily) or ciprofloxacin (500 mg orally twice daily).[2] A total of 835 subjects traveling to India, Guatemala, or Ecuador were enrolled in the trial. Most of the study centers (89%) were located in India.[2] Inclusion and exclusion criteria were similar to Trial 1, although Trial 2 excluded subjects traveling from the United States, Canada and Australia for reasons that were not clearly stated in the FDA summary report.[3] Most to the travelers in Trial 2 originated in Europe.[3] Safety and efficacy were evaluated at Visit 2 (day 2), Visit 3 (day 4 or 5), and the final visit (day 6). Stool samples were collected at the baseline visit and the end of treatment visit and sent to a central laboratory for pathogen identification and antibiotic susceptibility testing. If a patient received rescue therapy within 120 hours after ingestion of the first dose of the study drug, the patient was considered a treatment failure.[2]

The primary endpoint for Trial 2 was TLUS as documented by subjects in a daily diary over 5 days, which was similar to Trial 1.[2] The median TLUS for ciprofloxacin-treated patients was assumed as 27.5 hours and 28.5 hours for rifamycin.[2] The non-inferiority margin was defined by a maximally acceptable difference in the median TLUS of 8.5 hours (with a corresponding delta = 0.764 for the hazard ratio) between rifamycin and ciprofloxacin.[2] The confirmatory non-inferiority test was performed on the per-protocol (PP) analysis set and confirmed with a sensitivity test of the intention-to-treat (ITT) population.[2] Patients with lack of compliance, intake of forbidden concomitant medication, violation of eligibility criteria or early discontinuation due to adverse effects without causal relationship with study drug, were excluded from the PP population.[2] In total, 835 patients were randomized and received at least one dose of study medication.[2] The PP population consisted of 767 subjects (8.1% attrition).[2]

The median TLUS in the PP analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035), indicating non-inferiority of rifamycin to ciprofloxacin.[2] In the ITT analysis, median TLUS in the rifamycin-treated group was 44.3 hours versus 40.3 hours in the ciprofloxacin-treated group (p=0.0011 for non-inferiority).[2] Clinical cure was defined as 24 hours with no clinical symptoms and no more than 2 soft stools or 48 hours without symptoms or any unformed stools.[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2] In addition, the percentage of patients requiring rescue therapy was similar in both groups (rifamycin 2.6% vs. ciprofloxacin 1%; p =0.072).[2] The most common pathogen identified from collected stool samples was *E. coli*, although in 37.1% of patients no pathogen could be isolated.[2] Additional information about Trial 1 and Trial 2 is summarized in **Table 3.**

Trial Limitations:

According to the FDA summary, data for both Phase 3 trials of rifamycin were of adequate quality.[3] For Trial 1, the investigators' analysis of the primacy efficacy endpoint was accurate, but the analyses for a number of secondary endpoints (e.g. treatment failure, microbiological cure points) were inaccurate.[3] The FDA reviewer noted that the "time to unformed stool" is a misnomer.[3] For example, if a participant had a watery stool at 12 hours, soft stools at 30 and 35 hours, with no additional unformed stools, fever, or enteric symptoms, then the participant achieved clinical cure prior to the unformed stools at 30 and 35 hours.[3] Therefore, the TLUS value is 12 hours, even though there were two subsequent unformed stools.[3] In addition, the FDA reviewer noted the definition of clinical cure seems inadequate, as it accounts for rescue medication administered by study physicians but ignores prohibited medications self-administered (e.g., loperamide) or prescribed or administered by non-study physicians (e.g., antibacterial drugs).[3] Since use of such prohibited medications prior to the achievement of clinical cure (as defined by the investigators) could have contributed to that achievement, ignoring the use of prohibited medications when assessing clinical cure confounds the attribution of cure to the study medication.[3] The FDA reviewer noted in Trial 1 that 2% of patients (n=4) took prohibited medications and 5% of subjects (n=10) took an additional 2 doses of medication (or 1 extra treatment day) in the rifamycin-treated arm of the ITT population.[3] The extra doses were supplied as a contingency reserve in case of loss or mishap. However, one primary investigator prescribed additional doses to 4 subjects due to continued symptoms. It is not clear why the other subjects took the extra doses.[3] In Trial 2, 2% of patients in both arms (rifamycin and ciprofloxacin) took prohibited

medications in the PP population set.[3] Nineteen subjects (4.5%) in the rifamycin arm and 13 subjects (3.1%) in the ciprofloxacin did not submit complete diary cards.[3]

An additional concern was the incorrect handling of missing TLUS observations due to incomplete diary recordings. For example, one subject in the rifamycin arm maintained the daily diary for only 24 hours and recorded no stools during that period, the investigator assigned that subject a censored TLUS of 24 hours, meaning that the true (but unobserved) TLUS value is larger than 24 hours.[3] However, it is possible that the participant's true TLUS value is 0.[3] This would be the case if the participant also had no unformed stools during hours 24-48, as then hours 0-48 would constitute a 48-hour qualifying period for clinical cure and clinical cure would be achieved at hour 0.[3] Hence, this participant's TLUS value should be censored at 0 hours rather than 24 hours.[3] Instances of censoring due to incomplete diaries could be cases of informative censoring.[3] Four subjects submitted incomplete symptom diaries in Trial 1.

Since the non-inferiority design of Trial 2 did not include a placebo arm, the investigators had to rely on the use of historical information to determine efficacy, which means the results should be interpreted with caution.[3] The FDA reviewers also noted the establishment of the non-inferiority margin using the hazard ratio was flawed.[3] In order to determine a hazard ratio corresponding to a median TLUS margin of 8.5 hours, the investigators made strong assumptions about the true value of the ciprofloxacin median TLUS value and about the distribution of the rifamycin and ciprofloxacin TLUS values.[3] It is highly implausible that a hazard ratio of 0.764 corresponds to a median margin of 8.5 hours, given the true but unknown ciprofloxacin median TLUS and the true but a priori unknown distributions of the rifamycin and ciprofloxacin TLUS values.[3] The specification of a hazard ratio does not accurately specify a non-inferiority margin.[3]

In summary, Trial 1 provides moderate quality evidence of the effectiveness of rifamycin in treating TD caused by non-invasive E.coli in adults who were not experiencing fever or bloody stools compared to placebo.[1] Trial 2 provides low quality evidence that rifamycin is non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] Rifamycin has a similar spectrum of activity as rifaximin. Both antibiotics have low systemic absorption and duration of therapy (3-day course of treatment). Similar to rifaximin, rifamycin shortens the course of TD by approximately 1 day.[3] The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than E.coli or complicated by fever and bloody diarrhea. The efficacy or safety of rifamycin has not been evaluated in pediatric patients.

Clinical Safety:
In phase 3 studies, headache and constipation were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater or equal to 2% and higher than placebo or ciprofloxacin.[3] Discontinuation of rifamycin due to adverse reactions occurred in 1% of patients during the 2 clinical trials (n=619 total enrollment).[16] The most frequent adverse reactions leading to discontinuation of rifamycin were abdominal pain (0.5%) and pyrexia (0.3%).[15] In Trial 1 (placebo-controlled), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=199) and with an incidence higher than in the placebo group was constipation (3.5% rifamycin, 1.5% placebo).[15] In Trial 2 (active comparator: ciprofloxacin), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=420) and with an incidence higher than in the ciprofloxacin group was headache (3.3% rifamycin, 1.9% ciprofloxacin).[15] No deaths occurred in either clinical trial.

Look-alike / Sound-alike Error Risk Potential: Rifaximin

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in symptoms (diarrhea, abdominal pain, nausea)
2) Resolution of symptoms (clinical cure)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to last unformed stool (TLUS)
2) Percentage of patients with a clinical cure (two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period)

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription. This results in inhibition of bacterial synthesis and growth of bacteria.
Oral Bioavailability	Minimal systemic absorption: less than 0.1% oral bioavailability
Distribution and Protein Binding	Protein Binding: 80%
Elimination	Fecal: 86%
Half-Life	Unknown
Metabolism	Not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/N NT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dupont, et al.[1] Phase 3 RCT, DB, MC, PC N=264	1. Rifamycin 400 mg orally twice daily for 3 days 2. Placebo orally twice daily for 3 days	Demographics: 1. Median age: 24 yo 2. 50% female 3. Duration of diarrhea: 33 hrs. 4. Country visited: Mexico - 66% Guatemala - 34% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Taking an antibiotic against gram negative bacteria within 7 days	ITT: (all subjects who received 1 dose of medication) 1. 199 2. 65 PP: (all subjects that completed the trial) 1. 179 2. 53 Attrition: 1. 21 (10.6%) 2. 12 (18.5%)	Primary Endpoint: Length of time to TLUS 1. 46 hrs. 2. 68 hrs. Difference = 22 hours; p=0.0008 95% CI not able to be calculated Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 163 (81.4%) 2. 37 (56.9%) Difference = 24.5% p=0.0001 95% CI 11.3 to 37.7	NA 24.5%/ 5	Study withdrawal due to AE 1. 1 (0.5%) 2. 9 (13.5%) Diarrhea 1. 20 (10%) 2. 11 (16.9%) Headache 1. 17 (8.5%) 2. 6 (9.2%) Constipation 1. 7 (3.5%) 2. 1 (1.5%) p value and 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 3:1 via blocks of 4 developed by an independent statistician. Stratified by site. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Blinding was not clearly described. Detection Bias: Unclear. Investigators and patients blinded to study medication via the blister packet in which medication was dispensed. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. Higher withdrawal in placebo group due to the need for rescue therapy which may lead to a more conservative estimate of effect. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Santarus. Several investigators received consulting fees from Santarus or were employed by Santarus. **Applicability**: Patient: Primarily applies to travelers in Mexico and Central America. Patients with fever or bloody diarrhea were excluded. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to placebo to demonstrate superiority. Active comparator could have been rifaximin or azithromycin to provide comparative safety/efficacy data to standard of care. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 8 centers in Mexico (n=175) and 2 in Guatemala (n=89).

2. Steffen, et al.[2] Phase 3 RCT, DB, MC N=835	1.Rifamycin 400 mg orally twice daily for 3 days 2.Ciprofloxacin 500 mg orally twice daily for 3 days	Demographics: 1. Median age: 35 yo 2. 50% female 3. Country visited: India - 96% Guatemala - 2% Ecuador – 2% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Resident of any country with high incidence rates of diarrhea 8. Travelers from the US, Canada, and Australia	ITT: (all subjects who received 1 dose of medication) 1. 420 2. 415 PP: (all subjects who completed at least 2 days of diary recordings) 1. 384 2. 383 Attrition: 1. 36 (8.5%) 2. 42 (10%)	Primary Endpoint: Noninferiority assessment of median length of time to TLUS in PP population 1. 42.8 hrs. 2. 36.8 hrs. p=0.0035 for noninferiority HR = 0.943 95% CI 0.804 to 1.100 Noninferiority assessment of median length of time to TLUS in ITT population 1. 44.3 hrs. 2. 40.3 hrs. P=0.0011 for noninferiority HR = 0.962 95% CI = 0.826 to 1.119 Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 357 (85.0%) 2. 352 (84.8%) Difference = 0.2% p=0.942 Requirement of Rescue Therapy 1. 11 (2.6%) 2. 4 (1%) Difference = 1.6% p=0.072	NA NA NS NS	Incidence of AEs 1. 62(14.8%) 2. 62 (14.9%) Incidence of ADRs 1. 34 (8.1%) 2. 31 (7.5%) Study withdrawal due to AE 1. 1 (<1%) 2. 0 p value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via blocks of 4 using a computer-generated list of numbers. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Investigators dispensed blinded study medication according to randomization schedule. Detection Bias: Unclear. Investigators and patients blinded to study medication via the package medication was dispensed in. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. 3% of patient withdrew due to lack of efficacy, or follow-up. 7-8% withdrew due to protocol deviations. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Dr. Falk Pharma GmBH. Several investigators received honoraria from Dr. Falk Pharma GmBH or were employed by Dr. Falk Pharma GmBH. **Applicability**: Patient: Primarily applies to travelers to India. Patients with fever or bloody diarrhea were excluded. Excluded U.S. travelers, which limits generalizability to U.S. subjects. Patients in this trial were on average 10 years older than Trial 1. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to ciprofloxacin to establish non-inferiority. No placebo armed included to assess efficacy of rifamycin. Active comparator could have been rifaximin to provide comparative safety/efficacy data with a similar antibiotic. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 17 centers in India (n=805), 1 in Guatemala (n=15) and 1 in Ecuador (n=15).

Abbreviations : AD = antidiarrheal; ADR = adverse drug event; AE = adverse effect; ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; Hrs. = hours; ITT = intention to treat; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; TLUS = time to last unformed stool; US = United States; YO = years old

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AEMCOLO safely and effectively. See full prescribing information for AEMCOLO.

AEMCOLO (rifamycin) delayed-release tablets, for oral use.
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
AEMCOLO is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in adults. (1.1)

Limitations of Use:
AEMCOLO is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or due to pathogens other than noninvasive strains of *E. coli*. (1, 5.1, 14)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AEMCOLO and other antibacterial drugs, AEMCOLO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria (1.2).

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of AEMCOLO is 388 mg (two tablets) orally twice daily for three days. (2.1)
- Take each dose with a glass of liquid. Do **NOT** take AEMCOLO concomitantly with alcohol. (2.1)
- AEMCOLO can be taken with or without food. (2.1)
- Swallow AEMCOLO tablets whole. Do NOT crush, break or chew the tablets. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Delayed-Release Tablets: 194 mg rifamycin. (3)

----------CONTRAINDICATIONS----------
AEMCOLO is contraindicated in patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents (e.g. rifaximin), or any of the components in AEMCOLO (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of Persistent or Worsening Diarrhea Complicated by Fever and/or Bloody Stool: AEMCOLO was not shown to be effective in patients with diarrhea complicated by fever and/or bloody stool or diarrhea due to pathogens other than noninvasive strains of *E. coli* and is not recommended for use in such patients. Discontinue use if diarrhea gets worse or persists more than 48 hours, and consider alternative antibacterial therapy. (1. 5.1)
- *Clostridium difficile*-associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 2%) are headache and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aries Pharmaceuticals Inc. at 888-ARIES-08 (888-274-3708) option 1 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised:11/2018

Rifaximin (Xifaxan®) and Rifamycin (Aemcolo®)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- 3 days for traveler's diarrhea caused by non-invasive strains of *E.Coli* for rifaximin or rifamycin.
- Up to 12 months for hepatic encephalopathy for rifaximin.

Requires PA:

- Rifaximin and Rifamycin

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and is the indication funded by OHP?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis traveler's diarrhea caused by non-invasive strains of E.Coli?	**Yes:** Go to #4	**No:** Go to # 5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. • Preferred products for traveler's diarrhea are dependent on traveler's destination and resistance patterns in that area. Refer to **Table 1** for adult treatment recommendations.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 3 days.
5. Is the request for rifaximin to prevent or treat hepatic encephalopathy?	**Yes**: Go to #6	**No**: Pass to RPh. Deny; not funded by OHP or for medical appropriateness
6. Is the patient currently managed with a regularly scheduled daily regimen of lactulose?	**Yes**: Go to #8	**No**: Go to #7
7. Does the patient have a contraindication to lactulose?	**Yes**: Go to #8	**No**: Pass to RPh Deny; medical appropriateness Note: studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose.
8. Is the patient currently prescribed a benzodiazepine drug?	**Yes**: Go to #9	**No**: Approve for up to 12 months

Approval Criteria		
9. Is the patient tapering off the benzodiazepine? Note: tapering process may be several months	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness Note: studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy**.**

Table 1. Acute diarrhea treatment recommendations for adults[1]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally **OR** 500 mg once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant enterotoxigenic *E. coli* are suspected.

b. Preferred regimen for dysentery or febrile diarrhea.

c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

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