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, April 1st, 2021 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
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	R. Citron (OSU)
	D. Department Update	D. Weston (OHA)
	E. Legislative Update	T. Douglass (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Oncology Prior Authorization Update	
	1. Public Comment	
	III. DUR NEW BUSINESS	
1:25 PM	A. Opioid Literature Scan/Policy Evaluation	
	1. Literature Scan	A. Gibler (OSU)
	2. Policy Evaluation	S. Servid (OSU)
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	
1:55 PM	B. Antipsychotics in Children DERP Summary/ Mental Health Polypharmacy Drug Use Evaluation	
	1. DERP Summary/Safety Edit	S. Fletcher (OSU)
	2. Drug Use Evaluation	S. Servid (OSU)
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	

IV. PREFERRED DRUG LIST NEW BUSINESS

2:20 PM	A. Imcivree™ (setmelanotide) Abbreviated Drug Review	
	1. Weight Loss Coverage State Plan Overview	D. Weston (OHA)
	2. Abbreviated Drug Review	S. Fletcher (OSU)
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	
2:30 PM	B. Lumizyme® (alglucosidase alfa) New Drug Evaluation	D. Engen (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
2:45 PM	BREAK	
3:00 PM	C. Neuromyelitis Optica Spectrum Disorder (NMOSD) Class Review	D. Moretz (OSU)
	1. Class Review and Prior Authorization Criteria	
	2. Uplizna™ (inebilizumab-cdon) New Drug Evaluation	
	3. Soliris® (eculizumab) New Drug Evaluation	
	4. Enspryng™ (satralizumab-mwge) New Drug Evaluation	
	5. Public Comment	
	6. Discussion of Clinical Recommendations to OHA	
3:25 PM	D. Monoclonal Antibody C5 Inhibitors Class Review	D. Moretz (OSU)
	1. Class Review/Prior Authorization Criteria	
	2. Ultomiris® (ravulizumab-cwvz) New Drug Evaluation	
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	
3:50 PM	E. Statins Class Update	M. Herink (OSU)
	1. Class Update	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
4:05 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
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
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
Tim Langford, PharmD, BCPS, CDE, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Oregon Health Forum	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 04, 2021 1:00 - 5:00 PM

Via Zoom webinar

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: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Cathy Zehrung RPh; Patrick DeMartino, MD; Cat Livingston, MD, MPH; Stacy Ramirez, PharmD; Tim Langford, PharmD, BCPS, CDE, USPHS; Caryn Mickelson, PharmD; Robin Moody, MPH; William Origer, MD, FAAFP.

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Dean Haxby, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Dee Weston, JD; Amanda Parrish, LCSW; Brandon Wells

Audience: Sami Nasrawi, Alnylam Pharmaceuticals*; Andrea Wilcuts, Takeda Pharmaceuticals; Brandi Ferger, Advanced Health; Camille Kerr, Regeneron; Chi Kohlhoff, Viela Bio; Christina Hartman; Crystal Cooper-Siegel, Alexion; **Debby Ham, Aimmune Therapeutics;** Erika Finanger, MD, OHSU; Eva Solis, Jean Ritter, Zealand Pharma; Jenny Todenhagen; Jerey Stand, Alexion; Jim Cromwell; Jim Graves, BMS; Katie Scheelar, Moda Health; **Kelly Maynard, Little Hercules Foundation***; Mark Kantor, AllCare Health; Matt Worth, OHSU; Timothy McFerron, Alkermes; Meganne Leach, PNP, OHSU; Michael Foster, BMS; Mike Nicholson; Norm Navarro, Providence; Paul Thompson, Alkermes; Rachel Hartman, IHN; Rebekah Bartholomew, OSU; Richard Dabner, Alnylam Pharmaceuticals; Rick Frees, Vertex; Suzanne Morgan, Tiffany Jones, PacificSource; **Tracy Copeland, Sarepta Therapeutics***; Wendy Bibeau, BMS. **Stephanie Yamamoto, Janssen Scientific Affairs***

(*) Provided verbal testimony

Written testimony: Posted to OSU Website

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I. CALL TO ORDER

A. The meeting was called to order at approximately 1:06 pm. Introductions were made by Committee members and staff
B. Conflict of Interest Declaration - No new conflicts of interest were declared
C. The Committee elected Stacy Ramirez as the chair and Bill Origer as the vice chair
D. Approval of December 2020 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all returning members in favor, new members abstained
E. Department and legislative update provided by Dee Weston

II. CONSENT AGENDA TOPICS

A. P&T Methods and Operating Procedures
B. Orphan Drug PA update
C. Oncology Policy Update
D. Anticoagulant Literature Scan
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

Public Comment: Sami Nasrawi, Alnylam Pharmaceuticals
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. Quarterly Utilization Report: Roger Citron, RPh
B. ProDUR Report: Rich Holsapple, RPh
C. RetroDUR Report: Dave Engen, PharmD
D. Oregon State Drug Review: Kathy Sentena, PharmD
- New Disease-Modifying Anti-Rheumatic Drugs for management of Rheumatoid Arthritis
- Cardiovascular Outcomes Associated with Newer Therapy Classes for Type 2 Diabetes Mellitus

IV. PREFERRED DRUG LIST NEW BUSINESS

A. **Duchenne Muscular Dystrophy (DMD) Class Update and DERP Report with New Drug Evaluation (NDE):** Sarah Servid, PharmD

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Recommendations:
- Update prior authorization (PA) criteria for DMD to include viltolarsen to ensure medically appropriate use
- Evaluate costs in executive session

Public Comment: Tracy Copeland, Medial Affairs, Sarepta Therapeutics; Kelly Maynard, Little Hercules Foundation

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

B. **Acne Class Update with NDE**: Sara Fletcher, PharmD

Recommendations:
- Designate clascoterone as non-preferred on the PDL
- Evaluate costs in executive session

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

C. **Treatments for Peanut Allergy:** Sara Fletcher, PharmD

Recommendations:
- Create "Peanut Desensitization" PDL class within Immunology
- Designate Palforzia as non-preferred based on clinical Information
- Implement PA criteria to ensue appropriate use of Palforzia for funded conditions

Public Comment: Debbie Ham, Medical Affairs, Aimmune Therapeutics

ACTION: The Committee recommended amending the proposed criteria to specify Epi use/ER visit/hospitalization associated with peanut exposure; to amend the renewal criteria to specify absence or reduction in ER visits/hospitalizations; and to rename the class "Immunotherapy Desensitization" so not specific to only peanuts

Motion to approve, 2nd, all in favor

D. **Smoking Cessation Literature Scan:** Dave Engen, PharmD

Recommendation:
- No PDL changes recommended based on the clinical evidence
- Update PA criteria to allow varenicline therapy for two 12-week treatment regimens within 1 year for patients 17 years of age and older
- Evaluate costs in executive session

ACTION: The Committee recommended removing the PA requirement from preferred products

Motion to approve, 2nd, all in favor

E. **Antidepressant Class Update:** Sarah Servid, PharmD

Recommendation:
- No PDL changes recommended based on the clinical evidence
- Update esketamine safety edit to accommodate new indication
- Evaluate costs in executive session

Public Comment: Stephanie Yamamoto, Janssen Scientific Affairs

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ACTION: The Committee recommended amending the renewal criteria to include an assessment of adherence to oral antidepressant therapy
Motion to approve, 2nd, all in favor

F. **Non-Steroidal Anti-Inflammatory Drug (NSAID) Class Update**
Recommendation:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Cathy Zehrung RPh; Patrick DeMartino, MD; Cat Livingston, MD, MPH; Stacy Ramirez, PharmD; Tim Langford, PharmD, BCPS, CDE, USPHS; Caryn Mickelson, PharmD; Robin Moody, MPH; William Origer, MD, FAAFP

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Dee Weston, JD; Brandon Wells

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Anticoagulant Literature Scan:**
Recommendation: Make dalteparin syringes non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **Duchenne Muscular Dystrophy Class Update:**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

C. **Acne Class update**:
Recommendation: Make benzoyl peroxide (BPO) lotion and erythromycin/BPO gel preferred; and make BPO towelette non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

D. **Smoking Cessation Literature Scan**:
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

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E. **Antidepressants Class Update**:
Recommendation: Make duloxetine DR capsules, bupropion HCL XL 24H tablets (Wellbutrin XL & associated generics), and desvenlafaxine succinate ER 24H tablets preferred; and make amoxapine tablets voluntary non-preferred. Explore RetroDUR opportunities for dose consolidation with vortioxetine and change forms to switch utilization from desvenlafaxine 24H ER tabs to desvenlafaxine succinate 24H ER tabs
ACTION: Motion to approve, 2nd, all in favor

F. **NSAID Class Update**:
Recommendation: Make celecoxib (brand and generic) preferred. Make Qmiiz ODT, flurbiprofen and ketorolac tablets non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

IX. ADJOURN

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Prior Authorization Criteria Update: Oncology

Purpose of the Update:
This update identifies antineoplastic drugs recently approved by the FDA to add to the oncology policy (see **Table 1).**

Table 1. New oncology drugs

Generic Name	Brand Name
Azacitidine	ONUREG
Lisocabtagene maraleucel	BREYANZI
Olatuzumab vedotin-piiq	POLIVY
Ponatinib	ICLUSIG
Tepotinib	TEPMETKO
Trilaciclib	COSELA
Umbralisib	UKONIQ

Recommendation:

- Modify PA to include new, recently approved antineoplastic drugs.

Appendix 1. Proposed Prior Authorization Criteria

Oncology Agents

Goal(s):
To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.

Length of Authorization:

- Up to 1 year

Requires PA:

Initiation of therapy for drugs listed in **Table 1** (applies to both pharmacy and physician administered claims). This does not apply to oncologic emergencies administered in an emergency department or during inpatient admission to a hospital.

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 request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #6

Approval Criteria		
6. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #8
8. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Table 1. Oncology agents which apply to this policy (Updated 03/02/2021)

New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
alpelisib	PIQRAY
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS

Generic Name	Brand Name
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO

Generic Name	Brand Name
ibrutinib	IMBRUVICA
idelalisib	ZYDELIG
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA

Generic Name	Brand Name
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sonidegib phosphate	ODOMZO
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tepotinib	TEPMETKO

Generic Name	Brand Name
tisagenlecleucel	KYMRIAH
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA

Generic Name	Brand Name
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20

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Drug Class Literature Scan: Long and Short-acting Opioids

Date of Review: April 2021

Date of Last Review: February 2020
Literature Search: 01/01/2020 – 01/15/2021

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

Conclusions:
- Several systematic reviews were published in 2020 covering a various pain conditions, populations and opioid therapies, including reports from the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality (AHRQ) and the Canadian Agency for Drugs and Technologies in Health (CADTH).
- The American College of Rheumatology and the Arthritis Foundation, The American College of Physicians and American Academy of Family Physicians, and the Department of Veterans Affairs and Department of Defense all published clinical practice guidelines related to opioid therapy and pain management in 2020.
- Two new opioid formulations were approved by the U.S. Food and Drug Administration (FDA):
    - PROLATE (oxycodone/acetaminophen), a tablet that contains 5, 7.5, or 10 mg of oxycodone combined with 300 mg of acetaminophen; and
    - QDOLO (tramadol), a short-acting tramadol 5 mg/mL oral solution product.
- Current Oregon Health Plan (OHP) Fee-for-Service (FFS) Preferred Drug List (PDL) and opioid policies are supported by the evidence identified in this drug class literature scan.

Recommendations:
- No further research needed at this time. Update current policy with new drug product approvals.

Summary of Prior Reviews and Current Policy
Current evidence supports modest improvements in pain and function with use of opioids for acute pain or chronic non-cancer pain compared to placebo (high quality evidence). No difference in pain or functional status has been consistently observed between opioids and non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain (low to moderate quality evidence).

Overall, evidence is limited by short follow-up and exclusion of patients at high risk for adverse events, such as opioid overdose and death. Current high quality guidelines recommend opioid therapy be reserved for patients with proven medical necessity and those who have failed non-opioid analgesic therapy. Chronic opioid therapy should only be considered with documented improvement in pain and function, thorough assessment of risks and benefits of therapy, and with appropriate ongoing monitoring.

Author: Andrew Gibler, PharmD

Oregon Health Plan (OHP) FFS prior authorization (PA) criteria limit short-acting opioid prescriptions to 7 days and no more than 90 milligram morphine equivalents (MME) per day (see Appendix 5). Quantity limits allow up to 2 prescriptions every 90 days without a PA. All prescriptions for long-acting opioids require a PA. For authorization of chronic opioid therapy, providers are required to document sustained improvement from treatment, review the PDMP to verify appropriate prescribing patterns, conduct a recent urine drug screen to assess use of illicit drugs, and assess risk of concurrent central nervous system depressants.

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:

Agency for Healthcare Research and Quality U.S. Department of Health and Human Services: Opioid Treatment for Chronic Pain (2020)
In 2013, the Agency for Healthcare Research and Quality (AHRQ) commissioned a comparative effectiveness review on the risks and benefits of opioid therapy for chronic pain, focusing on studies with long-term (≥12 months) follow-up.[1] The 2014 AHRQ report found insufficient evidence to show benefits of long-term opioid therapy for chronic pain but found that long-term opioid use was associated with increased risk of overdose, opioid abuse, and other harms.[1] This AHRQ report was used as the basis for developing the 2016 CDC guidelines on opioids for chronic pain.[2]

This 2020 AHRQ report updates the 2014 report, including efficacy (related to pain, functioning and quality of life) and harms (related to opioid use disorder, overdose, and specific adverse events) associated with short-term (1 to <6 months), intermediate-term (6 to <12 months), and long-term follow-up (≥12 months), comparisons with nonopioid therapies, dose strategies, dose-response relationships, risk mitigation strategies, discontinuing and tapering of opioid therapy, and population differences (e.g., specific type of pain, patient demographics, and patient comorbidities).[3] This review is one of 3 concurrent AHRQ systematic reviews on treating chronic pain; the other reviews address non-pharmacological treatments[4] and non-opioid pharmacological treatments[5].

The methods for this systematic review follow the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[6] The review protocol and the full report provide additional methodological detail. Inclusion and exclusion criteria were developed a priori based on the Key Questions and PICOTS (Population, Interventions, Comparators, Outcomes, Timing, and Setting) and are detailed in Table 1 of the report and the published protocol.[3] Briefly, the following inclusion criteria were applied: 1) randomized controlled trials (RCTs) reporting outcomes at least 1 month following completion of treatment; 2) studies that compared opioids with placebo or no intervention, nonopioids, or different opioids, as well as studies that compared opioids plus nonopioids with opioids and nonopioids;

and 3) studies that assessed at least one of the following outcomes of interest: pain, function, health status/quality of life, mental health outcomes, sleep, doses of opioid used (for comparisons involving opioids and nonopioid therapy) and harms.[3] Study quality was independently assess by two investigators using predefined criteria: RCTs were evaluated using criteria and methods developed by the Cochrane Back and Neck Group;[7] cohort and other observational studies of interventions were evaluated using criteria developed by the U.S. Preventive Services Task Force;[8] and studies of diagnostic accuracy were assessed using Quality Assessment of Diagnostic Accuracy Studies – Version 2 (QUADAS-2).[9] These criteria were used in conjunction with the approach recommended in the AHRQ Methods Guide.[6]

A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0 to 10-point numeric rating scale or visual analog scale (VAS), and for function as a standard mean difference (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent.[3] A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0 to 100-point VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent.[3] Large effects were defined as greater than moderate.[3] The overall strength of evidence for each outcome was graded high, moderate, low, or insufficient based on study limitations; consistency of results across studies; the directness of the evidence linking the interventions with health outcomes; effect estimate precision; and reporting bias.[3]

The report included 115 RCTs and 40 observational studies.[3] Included observational studies were restricted to those that controlled for potential confounders.[3] Evidence from RCTs was almost exclusively restricted to trials ≤6 months in duration, and most trials had methodological shortcomings.[3] Few studies evaluated how benefits and harms vary in subgroups defined by demographic characteristics, characteristics of the pain condition, medical or psychological comorbidities, and substance use history.[3] A summary of the key opioid-related outcomes evaluated is illustrated in the table below.

Table 1. Summary of Findings Adapted from AHRQ Report.[3]

Key Effectiveness Outcome	Summary Findings
Opioids vs. placebo or no opioid	• Opioids were associated with a small mean improvement vs. placebo in pain intensity at short-term follow up (71 trials, N=19,616; MD -0.79 point on a 0 to 10 scale, 95% CI, -0.93 to -0.67, I^2=71%, SOE: high). • Opioids were associated with increased likelihood vs. placebo of experiencing a pain response at short-term follow up (44 trials, N=12,481; RR 1.35, 95% CI, 1.24 to 1.48; I^2=81%; ARD 15%, 95% CI, 11% to 19%; SOE: high). • Opioids were associated with a small mean improvement vs. placebo in function at short-term follow up (44 trials, N=12,427; SMD -0.22, 95% CI, -0.28 to -0.16, I^2=53%; SOE: high). • Opioids were associated with a mean improvement below the threshold for small vs. placebo in SF-36 measures of physical health status at short-term follow up (23 trials, N=8,005; MD 1.64 points on a 0 to 100 scale, 95% CI, 1.10 to 2.17, I^2=0%; SOE: high). • No difference was found between opioids vs. placebo in mean improvement on SF-36 measures of mental health status at short-term follow up (21 trials, N=7,586; -0.48 point on a 0 to 100 scale, 95% CI, -1.39 to 0.44, I^2=65%, SOE: high) • Opioids were associated with a small mean improvement vs. placebo in sleep quality at short-term follow up (25 trials, N=6,720; SMD -0.25, 95% CI, -0.32 to -0.19, I^2=11%; SOE: moderate).

Opioid effectiveness depending on: specific type or cause of pain; patient demographics; patient comorbidities; or type of opioid	• Effects of opioids vs. placebo on mean improvement in pain were greater at short-term follow up in trials of patients with neuropathic pain (20 trials, N=2568) than musculoskeletal pain (50 trials, N=16,979), with a difference of 0.5 point on a 0 to 10 scale (SOE: low). • Limited evidence found similar effects of opioids vs. placebo when analyses were stratified by age (4 trials), sex (2 trials), and race (1 trial) (SOE: low). • Analyses of 70 placebo-controlled trials found no interactions between type of opioid on short-term pain, function, SF-36 health status, sleep, depression, or adverse effects; 5 trials directly comparing different types of opioids found a mixed mechanism agent associated with greater pain relief vs. a pure opioid agonist with fewer side effects and 3 trials that directly compared a partial vs. pure opioid agonist found no differences between a partial vs. pure opioid agonist (SOE: moderate).
Opioid vs. nonopioid	• No differences were found between opioids vs. nonopioids in mean improvement in pain (14 trials, N=2,195; MD -0.29 on a 0 to 10 scale, 95% CI, -0.61 to 0.03, I^2=62%) or likelihood of a pain response at short-term follow up (12 trials, N=2,886; RR 1.28, 95% CI, 0.90 to 1.85, I^2=94%) (SOE: moderate). • No differences were found between opioids vs. nonopioids in mean improvement in function at short-term follow up (11 trials, N=2,010; SMD 0.00, 95% CI, -0.14 to 0.12, I^2=26%) (SOE: high). • Opioids were associated with a greater improvement than nonopioids in SF-36 measures of physical health status at short-term follow up that was below the threshold for small (6 trials, N=1,423; MD -1.80 points on a 0 to 100 scale, 95% CI, -5.45 to -0.12, I^2=11%) (SOE: moderate). • No differences were found between opioids vs. nonopioids in SF-36 mental health status (6 trials, N=1,427; MD -0.63 point on a 0 to 100 scale, 95% CI, -4.27 to 0.91, I^2=38%), sleep (7 trials, N=1,694; SMD 0.02, 95% CI, -0.10 to 0.12, I^2=0%), anxiety (3 trials, N=414; SMD 0.00, 95% CI, -0.62 to 0.36, I^2=8.9%) or depression (7 trials, N=748; SMD 0.05, 95% CI, -0.09 to 0.22, I^2=0%) at short-term follow up (SOE: low for anxiety, moderate for other outcomes). • There were no interactions between nonopioid type and effects on any short-term outcome.
Opioid plus nonopioid vs. nonopioid	• No differences were found between an opioid plus nonopioid vs. a nonopioid alone in mean improvement in pain at short-term follow up (6 trials, N=628; MD -0.36 on a 0 to 10 scale, 95% CI, -1.14 to 0.53, I^2=70%), likelihood of a pain response (6 trials, N=765; RR 1.46, 95% CI, 0.76 to 2.74, I^2=91%), function (4 trials, N=549; SMD -0.26, 95% CI, -0.63 to 0.17, I^2=66%), or other outcomes (SOE: low for all outcomes).
Opioid plus nonopioid vs. opioid	• An opioid plus nonopioid was associated with greater improvement in pain at short-term follow-up vs. an opioid alone that was below the threshold for small (5 trials, N=623; MD -0.40, 95% CI, -0.72 to -0.07, I^2=0%) (SOE: low). • No statistically significant differences between an opioid plus nonopioid vs. an opioid alone in likelihood of a pain response were found (5 trials, N=831; RR 1.19, 95% CI, 0.97 to 1.68, I^2=76%) or mean improvement in function (4 trials, N=521; SMD -0.25, 95% CI, -0.49 to 0.09, I^2=28%) (SOE: low). • No differences between an opioid plus nonopioid vs. an opioid alone in mean improvement in SF-36 measures of physical or mental health status, sleep, anxiety, or depression, though analyses were limited by small numbers of trials (SOE: low).

	• Four trials of patients with neuropathic pain found an opioid plus nonopioid associated with lower doses of opioid used (difference 5 to 13 mg MED/day) vs. an opioid alone, with pain relief better by 0.3 to 0.9 point with combination therapy (SOE: low). • One cohort study of patients with chronic pain prescribed opioids found no association between degree of self-reported cannabis use and pain, function, likelihood of opioid discontinuation, or opioid dose through up to 4 years of follow up; cannabis use was associated with increased anxiety (SOE: low).
Key Harms Outcome	Summary Findings
Harms of opioids vs. placebo or no opioid	• Opioids were associated with increased risk of discontinuation due to adverse events vs. placebo at short-term follow up (61 trials, N=19,994; RR 2.25, 95% CI, 1.86 to 2.73, I^2=72%; ARD 10%, 95% CI, 7% to 12%; SOE: high). • No difference between opioids vs. placebo in risk of serious adverse events at short-term follow up (38 trials, N=13,160; RR 1.23, 95% CI, 0.88 to 1.74, I^2=36%; SOE: moderate) • Opioids were associated with increased risk of nausea (60 trials, N=19,718; RR 2.46, 95% CI, 2.17 to 2.80, I^2=50%; ARD 14%, 95% CI, 11% to 17%), vomiting (49 trials, N=17,388; RR 3.57, 95% CI, 2.98 to 4.34, I^2=15%; ARD 7%, 95% CI, 6% to 9%), and constipation (58 trials, N=19,351; RR 3.38, 95% CI, 2.96 to 3.92, I^2=21%; ARD 9%, 95% CI, 7% to 12%) vs. placebo at short-term follow up (SOE: high) • Opioids were associated with increased risk of somnolence vs. placebo at short-term follow up (52 trials, N=17,458; RR 2.97, 95% CI, 2.44 to 3.66, I^2=48%; ARD 9%, 95% CI, 7% to 12%; SOE: high). • Opioids were associated with increased risk of dizziness vs. placebo at short-term follow up (53 trials, N=18,396; RR 2.66, 95% CI, 2.37 to 2.99, I^2=0%; ARD 8%, 95% CI, 6% to 10%; SOE: high). • Opioids were associated with increased risk of pruritus vs. placebo at short-term follow up (30 trials, N=11,454; RR 3.51, 95% CI, 2.47 to 5.16, I^2=50%; ARD 7%, 95% CI, 4% to 10%; SOE: high). • Opioids were not associated with increased risk of headaches vs. placebo at short-term follow up (48 trials, N=17,405; RR 1.06, 95% CI, 0.95 to 1.17, I^2=0%; SOE: high). • Two cohort studies found an association between opioid use and increased risk of opioid abuse, dependence, or addiction (SOE: low). • Two cohort studies found an association between opioid use and increased risk of overdose events (SOE: low). • One cohort study found prescription of long-acting opioids associated with increased risk of all-cause mortality vs. nonopioid medications (SOE: low). • Six observational studies found an association between opioid use and risk of fracture and 3 observational studies found an association between opioid use and risk of falls, though differences were not statistically significant in all studies and estimates decreased with longer duration of opioid use in some studies (SOE: low). Data could not be pooled due to significant heterogeneity. • Two observational studies found an association between opioid use and increased risk of myocardial infarction (SOE: low). • One cross-sectional study of men with back pain found long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs. nonuse (SOE: low).

	• One cohort study found no association between any long-term opioid use and increased risk of attempted suicide/self-harm (SOE: low).
Opioid harms depending on: (1) the specific type or cause of pain; (2) patient demographics; (3) patient comorbidities; (4) the dose of opioids used and duration of therapy; (5) opioid type; (6) use of sedative hypnotics; (7) use of gabapentinoids; and (8) use of marijuana.	• Analyses of placebo-controlled trials found no interactions between the pain type and risk of harms (SOE: low). • Evidence was too limited to determine effects of patient demographics and comorbidities on risk of harms (SOE: insufficient). • Three cohort studies found an association between concurrent use of benzodiazepines and opioids vs. opioids alone; in one study the risk of overdose decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids vs. opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low). <u>Dose/duration</u> • Analyses of placebo-controlled trials indicated no interaction between higher opioid dose category and increased risk of short-term harms; trials directly comparing higher vs. lower dose were limited but reported similar findings (SOE: low). • Two cohort studies found higher doses of long-term opioid therapy associated with increased risk of opioid abuse, dependence, or addiction compared with lower doses (SOE: low). • Four observational studies consistently found an association between higher doses of long-term opioids and risk of overdose or overdose mortality (SOE: low). • One cohort study found higher dose of opioids associated with increased risk of all-cause mortality; longer duration was associated with decreased risk of all-cause mortality (SOE: low). • Three observational studies reported inconsistent findings regrading a dose-response association between opioids and risk of fractures (SOE: insufficient). • One cohort study found modest associations between higher dose of long-term opioid and increased risk of falls and major trauma (SOE: low). • Two cohort studies reported inconsistent findings regarding a dose-response association between opioids and risk of cardiovascular events (SOE: insufficient). • One case-control study found an opioid dose greater than 20 mg MED/day in vehicle drivers is associated with increased odds of road trauma injury. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to less than 20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs, and number of physician and ED visits was 1.21 (95% CI, 1.02 to 1.42) for 20 to 49 mg, 1.29 (95% CI, 1.06 to 1.57) for 50 to 99 mg, 1.42 (95% CI, 1.15 to 1.76) for 100 to 199 mg, and 1.23 (95% CI, 1.02 to 1.49) for 200 mg or more (SOE: low). • Three cohort studies found association between higher opioid dose and risk of various endocrinological adverse events (use of erectile dysfunction medications or testosterone replacement, androgen deficiency, or female reproductive dysfunction) (SOE: low). • One cohort study found an association between longer duration of therapy and increased risk of new-onset depression; there was no association between higher dose and increased risk. A smaller study by the same authors reported similar findings for treatment-resistant depression (SOE: low).

	• Evidence from one cohort study was insufficient to determine the association between higher opioids doses and risk of attempted suicide/self-harm, due to the small number of events and imprecise estimates (SOE: insufficient). <u>Co-prescription of benzodiazepines or gabapentinoids (gabapentin and pregabalin)</u> • Three cohort studies found an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk of overdose; in one study, the risk decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low).
Harms of opioid vs. nonopioid	• Opioids were associated with increased risk of discontinuation due to adverse events (12 trials, N=3,637; RR 2.18, 95% CI, 1.48 to 3.08, I^2=43%; ARD 9%, 95% CI, 5% to 11%), somnolence (12 trials, N=3,377; RR 2.77, 95% CI, 2.09 to 4.18, I^2=13%; ARD 12%, 95% CI, 7% to 18%), nausea (11 trials, N=3,137; RR 2.77, 95% CI, 2.09 to 4.18, I^2=13%; ARD 12%, 95% CI, 7% to 18%), constipation (12 trials, N=3,377), vomiting (6 trials, N=2,644; RR 4.62, 95% CI, 2.94 to 7.24, I^2=0%; ARD 5%, 95% CI, 4% to 7%), pruritus (5 trials, N=2,577; RR 4.22, 95% CI, 2.45 to 8.20, I^2=0%; ARD 5%, 95% CI, 4% to 7%), and headache (8 trials, N=2,759; RR 1.35, 95% CI, 1.08 to 1.70, I^2=0%; ARD 3%, 95% CI, 1% to 5%) vs. a nonopioid at short-term follow up (SOE: moderate [discontinuation due to adverse events, constipation, somnolence] to high [nausea, vomiting, headache, pruritus]).
Harms of opioid plus nonopioid vs. nonopioid	• An opioid plus nonopioid was associated with increased risk of nausea (5 trials, N=330; RR 2.18, 95% CI, 1.16 to 6.49, I^2=0%; ARD 7%, 95% CI, 2% to 12%), constipation (6 trials, N=633; RR 2.74, 95% CI, 1.28 to 7.44, I^2=70%; ARD 23%, 95% CI, 7% to 41%) and somnolence (5 trials, N=330; RR 2.44, 95% CI, 1.32 to 4.52, I^2=0%; ARD 11%, 95% CI, 4% to 17%) vs. a nonopioid alone at short-term follow up. Effects on risk of discontinuation due to adverse events were not statistically significant (6 trials, N=707; RR 1.99, 95% CI, 0.89 to 4.26, I^2=34%). (SOE: low for discontinuation due to adverse events, moderate for nausea, constipation, and somnolence).
Harms of opioid plus nonopioid vs. opioid	• No differences between an opioid plus nonopioid vs. an opioid alone in risk of discontinuation due to adverse events (5 trials, N=782; RR 0.79, 95% CI, 0.50 to 1.27, I^2=0%), nausea (5 trials, N=585; RR 0.98, 95% CI, 0.57 to 1.84, I^2=0%), constipation (6 trials, N=860; RR 0.91, 95% CI, 0.67 to 1.13, I^2=0%), or somnolence (6 trials, N=860; RR 0.72, 95% CI, 0.35 to 1.33, I^2=58%),) vs. an opioid alone at short-term follow-up.
Dosing Strategies	Summary Findings
Short-acting vs. long-acting opioid	• Two trials found no differences in effectiveness or harms between long- vs. short-acting formulations of the same opioid administered at similar doses (SOE: low). • A cohort study found long-acting opioid associated with increased risk of overdose vs. short-acting opioids (HR 2.33, 95% CI, 1.26 to 4.32); risk decreased with longer duration of exposure (SOE: low).
Different long-acting opioids	• Four trials (N=2721) of long-acting oxycodone vs. tapentadol reported mean differences in pain that ranged from -0.1 to -1.0 on a 0 to 10 scale, but the dose was lower in the oxycodone arms (range in differences 35 to 45 mg MED/day); oxycodone was associated with increased risk of discontinuation due to adverse events and gastrointestinal adverse events, with no difference in risk of serious adverse events (SOE: low). • Three trials (N=1405) compared similar doses of long-acting oxycodone vs. morphine; effects on pain, SF-36 physical and mental health; adverse events were inconsistent, with some trials reporting no differences (SOE: low).

	• Three trials (N=957) compared transdermal fentanyl vs. long-acting morphine. Two trials reported no differences in pain or other outcomes. The third trial found a small difference in reduction pain intensity favoring transdermal fentanyl (difference about 5 points on a 0 to 100 scale). Two trials found a lower likelihood of constipation with transdermal fentanyl than long-acting morphine but discontinuations due to adverse events were higher with transdermal fentanyl (SOE: low). • Other long-acting opioid comparisons were evaluated in one or two trials, with no differences in effects (SOE: low) • One cohort study of Medicaid patients with chronic pain found methadone was associated with increased risk of overdose (HR 1.57, 95% CI, 1.03 to 2.40) but not risk of death or overdose (HR 0.71, 95% CI, 0.46 to 1.08) vs. long-acting morphine. Another cohort study of Medicaid patients found methadone was associated with increased risk of out-of-hospital death (an indicator of overdose deaths or suddent unexpected death, potentially due to arrhythmia vs. morphine (HR 1.46, 95% CI, 1.17 to 1.83), but a cohort study of Veterans Affairs patients found methadone associated with decreased risk of mortality (HR 0.56, 95% CI, 0.51 to 0.62) (SOE: low).
Opioid dose escalation vs. dose maintenance or use of dose thresholds	• One trial of more liberal dose escalation vs. maintenance of current doses found no difference in outcomes related to pain, function, or risk of discontinuation due to opioid misuse, but opioid doses were similar (52 vs. 40 mg MED/day at the end of the trial) (SOE: low).
Decreasing opioid doses or tapering off opioids vs. continuation of opioids	• One trial found a taper support intervention associated with no difference vs. usual care at 22 weeks in BPI pain severity (4.72 vs. 5.77, adjusted MD -0.68 on a 0 to 10 scale, 95% CI, -2.01 to 0.64), but greater improvement in BPI pain interference (adjusted MD -1.39 on a 0 to 10 scale, 95% CI, -2.78 to -0.01); effects persisted at 34-week follow up. Effects on opioid dose were not statistically significant (99.51 vs. 138.2 mg MED/day, adjusted difference -26.7, 95% CI, -83.0 to 29.6) (SOE: low).
Different tapering protocols and strategies	• One trial of patients undergoing tapering in a 15-day intensive outpatient interdisciplinary pain program found no differences between varenicline vs. placebo as an adjunct to tapering in median time to tapering completion, opioid withdrawal symptoms, pain, or depression (SOE: low). • One cohort study of patients prescribed 120 mg MED/day or more of long-term opioid therapy found, after controlling for sociodemographic and clinical factors, that each additional day to discontinuation was associated with a 1% lower risk of an emergency department visit or hospitalization with a diagnosis of opioid poisoning or a substance use disorder (equivalent to a 7% lower risk for each additional week to discontinuation) (SOE: low).
Different opioid dosages and durations of therapy	• In head-to-head trials, opioid doses of 50 to 90 mg MED/day were associated with a minimally greater (below the threshold for small) improvement mean pain intensity versus doses less than 50 mg MED/day (5 trials, N=2,625; MD -0.26, 95% CI, -0.57 to -0.02, I^2=38%); there was no difference in mean improvement in function. Analyses of placebo-controlled trials also found an interaction (p=0.009) between higher opioid dose and greater improvement in mean pain intensity, with some evidence of a plateauing effect at 50 mg or greater MED/day (SOE: moderate). • In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months (65 trials N=17,373; MD -0.83 on a 0 to 10 scale, 95% CI, -0.96 to -0.70, I^2=69%) than at 3 to 6 months (8 trials, N=2,243; MD -0.30, 95% CI, -0.83 to 0.23, I^2=78%); similar patterns were observed for likelihood of pain response and mean improvement in function (SOE: low).
Risk Mitigation	Summary Findings

Risk mitigation strategies	• One cohort study found co-prescription of naloxone in patients prescribed opioids for chronic pain associated with no difference between no naloxone in all-cause mortality (2.5% vs. 3.3%, RR 0.77, 95% CI, 0.45 to 1.31) or opioid poisoning deaths (0.3% vs. 0.2%, RR 1.08, 95% CI, 0.18 to 6.4), though naloxone co-prescription was associated with decreased risk of emergency department visits at 1 year follow up (RR 0.37, 95% CI, 0.22 to 0.64) (SOE: low). • No study evaluated the effectiveness of other risk mitigation strategies vs. non-use of the risk mitigation strategy for improving outcomes related to misuse, opioid use disorder, and overdose.

Abbreviations: ARD = absolute risk difference; BPI = Brief Pain Inventory; CI = confidence interval; HR = hazard ratio; MD = mean difference; MED = morphine equivalent dose; N = number of participants from all trials; RR = relative risk; SF-36 = 36-Item Short Form Survey; SMD = standardized mean difference; SOE = strength of evidence.

Agency for Healthcare Research and Quality U.S. Department of Health and Human Services: Treatment for Acute Pain (2020)

A separate 2020 systematic review commissioned by AHRQ was conducted to evaluate the effectiveness and comparative effectiveness of opioids, nonopioids, and nonpharmacologic therapy in patients with specific types of acute pain, including effects on pain, function, quality of life, adverse events, and long-term use of opioids.[10] This review focused on the following acute pain conditions: low back pain, neck pain, other musculoskeletal pain, neuropathic pain, postoperative pain (excluding inpatient management of pain after major surgical procedures), dental pain, pain due to kidney stones, and pain due to sickle cell disease.[10]

Eligible studies for inclusion included RCTs of opioid therapy versus nonopioid therapy or nonpharmacologic therapy, nonopioid therapy versus nonpharmacologic therapy, nonpharmacologic therapy versus inactive controls (placebo, sham therapy, attention control, or a minimal intervention), and head-to-head trials of nonopioid therapy and nonpharmacologic therapy.[10] Observational studies that evaluated an association between being prescribed opioids for acute pain versus no opioids, and on factors influencing opioid prescribing for acute pain conditions, were also included.[10] The review focused on outpatient therapy initiated shortly before discharge (e.g., after surgery or in emergency department). Outcomes were analyzed at less than 1 day, 1 day to less than 1 week, 1 week to less than 2 weeks, 2 weeks to less than 4 weeks, and 4 or more weeks.[10]

This review included 183 RCTs and most had methodological limitations. Evidence did not suggest an increased risk of serious harms for any intervention, but studies were also not designed to assess serious harms.[10] Pain was the most commonly evaluated outcome with primarily small to moderate effect sizes.[10] Meta-analyses could not be conducted for most specific types of acute pain due to small number of studies, methodological limitations and study heterogeneity.[10] The magnitude of effects was classified as small, moderate or large, and strength of evidence was assessed.[10]

Kidney stone pain was assessed in 12 trials, which found a single dose of morphine is probably associated with increased likelihood of persistent pain in the first 24 hours, decreased likelihood of pain relief, increased likelihood of rescue medication use, and increased likelihood of adverse events versus an NSAID.[10] Findings were similar for a single dose of meperidine but use of this medication has fallen out of favor due to high risk of adverse events.[10]

Dental pain was assessed in 46 trials.[10] Overall, these studies showed that a single dose of an opioid plus acetaminophen might be associated with decreased pain and decreased likelihood of rescue or repeat medication use in the first 24 hours versus acetaminophen alone but is probably associated with increased risk of adverse events.[10] An opioid plus acetaminophen or NSAID was probably associated with a small to moderate increase in pain intensity versus an NSAID alone in the first 24 hours, with increased likelihood of rescue or repeat medication use and increased likelihood of adverse events (NSAID doses were lower in the opioid arm than the NSAID-only arm in some trials).[10]

Treatment of postoperative pain was evaluated in 47 trials.[10] These trials focused on treatment in the immediate postoperative period, usually before discharge.[10] In the first 24 hours, a multidose course of opioids was associated with increased likelihood of repeat or rescue medication use versus an NSAID.[10] Studies also showed that opioids might be associated with increased study withdrawal due to adverse events versus acetaminophen.[10] A prescription for an opioid for elective or minor surgery might also be associated with increased likelihood of long-term use versus not being prescribed an opioid.[10]

Studies that evaluated acute low back pain (n=38) found that there is likely no difference between an opioid versus an NSAID and there might be no difference versus a muscle relaxant.[10] Opioids were associated with increased risk of short-term adverse events (e.g., nausea, dizziness) but serious adverse events were uncommon because the studies were not designed to assess risk of overdose, opioid use disorder, or long-term harms.[10] However, a possible association was found in observational studies with being prescribed opioids and increased risk of long-term use, versus not being prescribed opioids.[10]

Treatment of acute peripheral neuropathy was evaluated in 2 trials, which showed an opioid might be associated with increased likelihood of improvement in pain versus gabapentin in acute herpes zoster with increased likelihood of constipation.[10] Otherwise, evidence for acute neuropathic pain was lacking.[10]

Evidence for management of acute sickle cell pain was insufficient based on methodological limitations of the 3 trials assessed.[10] Studies that evaluated acute musculoskeletal pain (n=30) also provided insufficient evidence on opioid therapy versus NSAID therapy.[10] No studies that evaluated acute neck pain (n=5) evaluated pharmacological therapy.[10]

<u>Agency for Healthcare Research and Quality U.S. Department of Health and Human Services: Prevention, Diagnosis, and Management of Opioids, Opioid Misuse, and Opioid Use Disorder in Older Adults (2020)</u>

Another systematic review commissioned by AHRQ sought to provide a framework for understanding how to reduce adverse events from opioid use in older adults.[11] The conceptual framework developed outlined the stages of care for older adults who require or use opioids, and factors impacting management decisions and patient outcomes.[11] The framework prioritizes 3 potential targets to determine factors associated with, and interventions for: 1) opioid prescription reduction where harms outweigh benefits; 2) prevention of opioid misuse and opioid use disorder; and 3) reduction of other opioid-related harms.[11]

For the purpose of this systematic review, older adults were defined as age 60 years or older.[11] A total of 41 studies with multivariable models of factors associated with opioid-related outcomes and 16 studies of interventions in older adults were included in the review from 5,933 citations.[11] The evidence from current literature on risk factors is sparse, particularly for the most relevant patient-centered outcomes.[11] More than half (22/41) of the multivariable analysis studies evaluated factors associated with long-term opioid use, which is not specifically a high-risk behavior and may indicate continuing pain symptoms, but does increase exposure and, therefore risk for opioid-related harms.[11] Prior or early postoperative opioid use, or greater amounts of prescribed opioids (high number of opioid prescriptions or higher opioid dose) were consistently and strongly associated (e.g., relative risk [RR] >2.0) with long-term opioid use.[11] Back pain, depression, concomitant use of NSAIDs, and fibromyalgia also had consistent, but weaker associations (e.g., RR <2.0, but statistically significant) with long-term use of opioids.[11]

Several factors were weakly associated with long-term opioid use, including benzodiazepine use, comorbidity scores, substance misuse, tobacco use and low income.[11] However, studies were mostly consistent that alcohol abuse and healthcare utilization were not associated with long-term opioid use.[11] Across 6 studies that evaluated opioid-related disorders such as opioid-use disorder and opioid misuse, 3 studies each found variable associations of opioid misuse with alcohol misuse and gender.[11] Age among older adults, Black race, dementia, rural/nonurban residence, prescription of long-acting opioids, unmarried status, and the use of muscle relaxants were also variably associated with long-term opioid use.[11]

All other evaluations of specific factors and outcomes of interest were evaluated by only one or two studies each.[11] These included factors associated with opioid use disorder, high-risk obtainment of opioid prescriptions, procuring multiple opioid prescribers, mental health outcomes, physical health outcomes, all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, emergency department visits, opioid overdose, all-cause death, opioid-related death, and nonopioid-related death.[11]

There is limited evidence on interventions directed at older adults.[11] Of the 16 studies of opioid-related interventions in older adults, 6 studies examined screening tools to predict opioid-related harms, but none of these tools have been tested in large, national populations of older adults to assess real-world results or clinical outcomes related to their use.[11] Two studies found that prescription drug monitoring programs are associated with less opioid use at the state level but did not address appropriate use of opioids.[11] Other studied interventions included multidisciplinary pain education for patients, an educational pamphlet for patients, implementation of an opioid safety initiative, provision of patient information and pain management training for clinicians, a bundle of educational modalities for clinicians, free prescription acetaminophen, a nationally mandated tamper-resistant opioid formulation, and motivational interview training for nursing students.[11] Few intervention studies evaluated pain or other patient-centered outcomes such as disability or functioning.[11] The research shows that more research is needed in older adults to establish factors associated with clinically relevant opioid-related outcomes, and to identify interventions to improve primary prevention (reduction of opioid-related harms), and treatment of existing opioid misuse or opioid use disorder.[11]

A systematic review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling older adults (2020)
In another systematic review, investigators evaluated the evidence for efficacy of opioids for chronic non-cancer pain in community-dwelling adults 65 years of age or older.[12] Studies in this systematic review were included if conducted in outpatient or community settings and residential aged care facilities.[12] Studies which combined data from older and younger adults but did not perform a separate subgroup analysis for older people were excluded.[12]

A total of 7 studies met inclusion criteria out of 956 originally identified through database searches.[12] Two studies were set in residential aged care facilities, and the remaining 5 were in community settings.[12] Four studies were cross-sectional in design, two were prospective and one was a retrospective chart review.[12] Sample size ranged from 10 to 10,372 individuals.[12]

A small cross-sectional community study of 21 people showed that 73% of participants reported pain relief after taking opioids, but opioid use was not associated with pain intensity and most of the participants still experienced moderate levels of pain despite taking regular opioids.[12] Opioid use also did not improve general activity, mood, walking ability or relationships in this study.[12] In a study of 652 community-dwelling individuals suffering chronic osteoarthritis of the knee/hip, people with severe osteoarthritis were more likely to be taking opioids despite reported ongoing severe pain.[12] One chart review of 10 retrospective cases attending a tertiary-care pain program showed a reduction in the average Numeric Pain Scale rating from 6.35 to 2.95 in carefully selected patients (people without contraindications and who were cognitively and physically able to take opioids or supervised).[12] A cross-sectional study investigating 115 older adults with dementia found that people with significant cognitive impairment and older age were more likely to experience untreated pain.[12] Of these, 15% had ongoing pain despite regular use of opioids.[12] All studies evaluated concluded that analgesia was underutilized and sub-therapeutic.[12]

An observational cohort study assessed analgesia use and prevalence of pain across a 6-month period in 350 nursing home residents.[12] Despite the use of regular analgesia, including non-opioid products, there was no change in pain symptoms from baseline to 6 months.[12] A longitudinal observational study of 10,372 nursing home residents over the age of 65 years reported significant improvement in activities of daily living and social engagement in those taking long-acting

opioids compared to short-acting opioids, but the total number of opioid prescriptions was low (short-acting 18.9% vs. long-acting 3.3%), and results were confounded by concurrent use of non-opioid analgesics.[12]

The investigators concluded that the evidence to support long-term use of opioids in older people with chronic non-cancer pain is limited.[12] Few trials have been conducted specifically with older adults and age-specific guidance is needed to address initial assessment of need, indications, monitoring and de-prescribing of opioids.[12]

The Canadian Agency for Drugs and Technologies in Health: Pharmacological Interventions for Chronic Pain in Pediatric Patients: A Review of Guidelines (2020)

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of evidence-based guidelines regarding pharmacological interventions for pediatric patients (aged 6 to 18 years) with chronic pain.[13] A review of guidelines from January 2015 to April 2020 was conducted because of limited evidence available with respect to this population, either due to lack of RCTs or few RCTs of low quality.[13] Pharmacological interventions such as acetaminophen, NSAIDs, antidepressants, anticonvulsants, and opioids have been used for treatment of chronic non-cancer pain in children and adolescent despite this lack of evidence.[13] Pathophysiological classifications of chronic pain in the pediatric population include nociceptive pain (somatic or visceral), neuropathic pain (from damage to or dysfunction of the peripheral or central nervous system) and idiopathic pain.[13] The most common chronic pain disorders in the pediatric population include primary headache, centrally mediated abdominal pain syndromes, and chronic/recurrent musculoskeletal and joint pain.[13]

Seven potentially relevant reports from 107 identified citations were retrieved for full-text review and assessed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.[13] Based on pre-selected criteria, only one relevant evidence-based guideline on the management of chronic pain in pediatric patients was included.[13] Recommendations on various pharmacological treatments, including opioids, were mainly based on expert opinion and strength of recommendations were not provided.[13] Opioids were rarely recommended for chronic pain because of their adverse effect profile and, if used, should be used as short a duration as possible.[13] Treatment with codeine was not recommended in children under 12 years of age, and should be avoided in adolescents, particularly those with respiratory problems or those who are rapid metabolizers of CYP2D6.[13]

A Systematic Review and Meta-Analysis of the Effectiveness of Buprenorphine for Chronic Pain (2020)

Buprenorphine, a partial opioid agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor with high affinity for both receptors, has been increasingly prescribed for the treatment of chronic pain, especially in patients with comorbid substance use disorders.[14] However, buprenorphine is approved for the management of pain and opioid use disorder (OUD), there is not a consensus with regard to its effectiveness as an analgesic.[14] Pain and substance use disorders co-occur frequently, yet research on risk mitigation strategies for OUD among chronic pain patients is sparse.[14] The purpose of this systematic review and meta-analysis was to examine the effectiveness of buprenorphine maintenance treatment in patients with chronic pain with or without a history of OUD.[14]

The included studies assessed pain intensity in chronic noncancer pain patients with or without OUD who had received buprenorphine via buccal, transdermal, and sublingual routes of administration.[14] RCTs, nonrandomized trials, and observational studies such as case-control or cohort studies were included in the review.[14] Articles including cancer-related pain were excluded.[14] No systematic reviews comparing the effectiveness of buprenorphine for chronic pain patients with and without OUD were identified.[14]

The methodological quality of eligible studies was assessed using the Cochrane Risk of Bias Tool for RCTs.[14] Standardized mean differences (SMD) and their standard deviations were used as effect measures because most outcomes were presented as continuous data (mean value or mean changes).[14] SMDs were used because outcomes were often measured using different scales.[14] For the meta-analysis, a random-effects model was used to calculate the pooled effect

size, with 95% confidence limits.[14] Heterogeneity was assessed using I^2 statistics for quantification and Cochran's Q for statistical significance.[14] The following descriptors were used to classify results of the meta-analysis: "Strong" indicated consistent findings in multiple (at least two) high- or moderate-quality studies; and "moderate" indicated consistent findings in multiple low-quality studies or one high- or moderate-quality study.[14]

Thirteen studies in patients with chronic non-malignant pain without OUD met inclusion criteria, of which 4 articles were excluded because of missing data regarding pain intensity.[14] The 9 remaining studies included 1,369 patients and were conducted in the U.S., Canada, U.K., Italy, Sweden, Korea, Hong Kong and the Philippines.[14] The mean age of the participants was 57.2 years.[14] The publication years ranged from 2009 to 2017.[14] The administration route of buprenorphine was mostly transdermal; one study was conducted with buccal buprenorphine and another with buccal and transdermal.[14] In 5 of the studies, the buprenorphine group was compared with either placebo (4 studies) or tramadol (one study).[14]

Five studies which included 856 patients with chronic non-malignant pain with OUD met inclusion criteria, with publication dates that ranged between 2012 and 2016.[14] These 5 studies were conducted in the U.S. and the mean age of the participants was 42.8 years.[14] Buprenorphine was administered sublingually with naloxone in all 5 studies.[14] One of the 5 studies used a comparison group (methadone active comparator group). Four of the studies were prospective and one study was retrospective.[14]

Patient-reported pain intensity was assessed using a numerical rating scale at baseline and at the end of buprenorphine or buprenorphine-naloxone treatment, both in the studies that assessed patients with OUD and those that assessed patients without OUD.[14] The duration of treatment varied from 2 weeks to 6 months, with only one study reporting data for over 6 months for patients with OUD.[14] The treatment period of the studies without OUD ranged between 4 weeks and 6 months.[14]

The meta-analysis of the evidence of buprenorphine for chronic pain in patients with OUD resulted in a reduction of pain (SMD = -0.54, 95% CI, -0.98 to -0.09, $p<0.5$) after buprenorphine administration.[14] Highly significant heterogeneity was observed across comparison effect sizes for pain intensity ($Q = 49.53$, $p<0.01$, $I^2 = 92.99\%$).[14] Based on Cohen categories, the effect size was small.[14]

The meta-analysis of the evidence of buprenorphine for chronic pain in patients without OUD resulted in a reduction of pain (SMD = -2.19, 95% CI, -2.88 to -1.51, $p<0.5$) after buprenorphine administration.[14] There was moderately significant heterogeneity that was observed across comparison effect sizes for pain intensity ($Q = 582.80$, $p<0.01$, $I^2 = 97.91\%$).[14] Based on Cohen categories, the effect size was moderate to large.[14]

This review provided evidence for analgesic effects of buprenorphine for patient with chronic noncancer pain with or without OUD.[14] However, weaknesses in the body of evidence prevent any strong conclusions due to substantial study heterogeneity because of variability in study design, dosing and route of administration of buprenorphine, thus preventing any strong conclusions.[14] Collectively, the evidence for substantial analgesic benefits was significantly stronger in the studies of chronic pain patients without OUD.[14] The small-sized effect (in a small number of studies) of buprenorphine on chronic pain in patients with a history of OUD suggests more research in this area is warranted.[14]

<u>The Canadian Agency for Drugs and Technologies in Health: Codeine for Pain Related to Osteoarthritis of the Knee and Hip: A Review of Clinical Effectiveness (2020)</u>

Osteoarthritis (OA) is the most common type of joint disease in older adults, and commonly involves the knees and hips.[15] The goal of OA management is to control pain and improve function with a combination of self-management techniques (e.g., physical exercise and weight management), medications, and

orthopedic surgery.[15] The objective of this CADTH report was to evaluate the clinical effectiveness of codeine with or without acetaminophen or an NSAID for patients with acute or chronic pain related to OA of the knee of hip.[15] Typical pharmacological options used for symptom management may include oral and topical NSAIDs, topical capsaicin, intraarticular glucocorticoid injections, acetaminophen, and opioids.[15] Codeine is a weak opioid that can be used in conjunction with non-opioid analgesics such as acetaminophen or NSAIDs.[15] Codeine is a prodrug that is metabolized to morphine by cytochrome P450 enzyme CYP2D6.[15] CYP2D6 polymorphisms are common across populations, different rates of codeine metabolism result in varying degrees of analgesia or adverse events.[15] Specifically, patients who are poor metabolizers of codeine may experience suboptimal pain control, while ultra-rapid metabolizers have a higher risk of adverse events.[15]

Two systematic reviews with meta-analyses and 3 RCTs were identified regarding the clinical effectiveness of codeine with or without acetaminophen or ibuprofen for patients OA-related pain of the knee or hip.[15] One systematic review contained 3 RCTs relevant to the CADTH report, which showed codeine had moderate benefit for pain (SMD -0.51; 95% CI, -1.01 to -0.01) and function (SMD -0.42; 95% CI, -0.74 to -0.10) compared to control groups (placebo or no codeine), but at significantly higher risk for early study withdrawal due to adverse events (RR 3.67; 95% CI, 2.16 to 6.24).[15] Findings from one RCT suggested reduced need for rescue pain medications with controlled-release codeine versus the control group, while the other 2 RCTs did not detect differences between codeine plus acetaminophen or ibuprofen versus control groups for this outcome.[15] All 3 RCTs found higher rates of adverse events (e.g., nausea, constipation) with codeine versus control groups, with statistically significant differences detected in 2 RCTs.[15] Limitations to this evidence included lack of reporting of respiratory depression in the literature, short follow-up from all 3 RCTs, and one trial co-authored by the drug manufacturer.[15] No RCTs have been conducted since 2000, or studies that compared codeine with or without acetaminophen or ibuprofen with different opioids or NSAIDs other than ibuprofen.[15]

A Systematic Review and Meta-Analysis of the Efficacy and Safety of Tapentadol Immediate Release for Acute Pain (2020)

The objective of another systematic review and meta-analysis was to examine the efficacy and safety of tapentadol immediate-release (IR) compared with other short-acting orally administered opioids for the management of acute pain.[16] Tapentadol is a synthetic μ-receptor agonist with effects on norepinephrine reuptake inhibition, similar to tramadol, but does not require metabolism via CYP2D6 enzyme which is subject to high variability in certain populations. Randomized controlled trials and observational studies that evaluated the efficacy and safety of tapentadol IR compared to other IR orally administered opioids in patients with acute pain were eligible for inclusion in this review.[16] Of the included studies, only RCTs that used oxycodone IR as a comparator were included in the meta- analysis.[16] Observational studies and studies including other opioid comparators (e.g., morphine, tramadol), were reviewed qualitatively.[16] Doses of tapentadol utilized in studies were stratified in the analysis into 4 groups: 50, 75, 100 mg and titrated dose (i.e., a titration strategy used in both groups).[16] The studies used different efficacy endpoints for pain outcomes.[16] Primary endpoints reported in the studies (i.e., pain) were standardized by calculating the standardized mean difference (SMD) (Hedges' *g*) with 95% CIs.[16] Studies that did not report the numeric value of the primary outcome measure were not included in the meta-analysis.[16] Safety outcomes were reported as numbers and proportions of the following common adverse effects of opioids: nausea, vomiting, constipation and dizziness.[16] Adverse events were reported as risk ratios (RRs) with 95% CIs.[16] Random effects models were used for all meta-analyses.[16] The heterogeneity among the studies was assessed using the I^2 statistic expressed as a percentage (higher percentages represent greater heterogeneity).[16]

Fourteen studies (n=12,814) were included in the systematic review, 13 of which were RCTs.[16] All 8 studies (n=3,706) included in the meta-analysis were double-blind RCTs.[16] Most of the studies included involved patients with acute postoperative pain; however, a few pertained to acute low back pain, osteoarthritic knee or hip pain, or acute pain in generalized hospitalized patients.[16] The pain outcomes assessed varied between studies and included the sum of pain intensity, the sum of pain intensity difference measured at 24, 48, 72 and 120 hours, mean total pain relief over 8 hours, or Numerical Pain Rating Scale.[16] Two studies were considered low risk of bias and 3 studies had high risk of bias; the remaining studies generated some concern of bias to the investigators primarily due to

randomization, allocation and blinding methods. Incomplete outcome data was the primary reason the investigators assessed a study as high risk of bias.[16] No evidence of publication bias was found by funnel plot.[16]

Tapentadol IR 50 mg was less effective at pain control than oxycodone IR (SMD 0.25; 95% CI, 0.06 to 0.44; p<0.01).[16] No differences were found between the 75 mg dose (SMD 0.11; 95% CI, -0.20 to 0.43; p=0.48), the 100 mg dose (SMD 0.20; 95% CI, -0.14 to 0.54; p=0.24) or the titrated dose group (SMD 0.01; 95% -0.11 to 0.14; p=0.83).[16] Heterogeneity ranged from none-to-moderate depending on the dose group: 50 mg (I^2=44%), 75 mg (I^2=77%), 100 mg (I^2 = 62%), titrated (I^2 = 0%).[16]

Tapentadol IR was associated with less nausea compared with oxycodone IR, with greatest effect in the lower dose groups: 50 mg (RR 0.60; 95% CI, 0.48 to 0.75; p<0.01), 75 mg (RR 0.61; 95% CI, 0.45 to 0.81; p<0.01), 100 mg (RR 0.82; 95% CI, 0.70 to 0.97; p=0.02).[16] However, there was no difference between the titrated dose groups of tapentadol IR and oxycodone IR were found (RR 0.84; 95% CI, 0.66 to 1.07; p=0.16).[16] Heterogeneity ranged from none-to-moderate for the dose groups (I^2 = 0% to 69%).[16]

The lowest dose of tapentadol IR (i.e., 50 mg) was associated with less vomiting compared with oxycodone IR (RR 0.39; 95% CI, 0.29 to 0.53; p<0.01).[16] However, as the dose of tapentadol increased no difference was found for all other doses: 75 mg (RR 0.60; 95% CI, 0.35 to 1.05; p=0.07), 100 mg (RR 0.78; 95% CI, 0.58 to 1.05; p=0.10), and titrated group (RR=0.89; 95% CI, 0.45 to 1.75; p=0.74).[16] Heterogeneity ranged from none-to-moderate for the dose groups (I^2 = 17% to 84%)[16]

Constipation was less with tapentadol IR for all dose groups compared to oxycodone IR: 50 mg (RR 0.44; 95% CI, 0.32 to 0.61; p<0.01), 75 mg (RR 0.31; 95% CI, 0.21 to 0.45; p<0.01), 100 mg (RR 0.62; 95% CI, 0.39 to 0.97; p=0.04), and titrated dose (RR 0.46; 95% CI, 0.29 to 0.73; p<0.01). Heterogeneity ranged from none-to-moderate for the dose groups (I^2 = 0% to 66%).[16]

Dizziness was lower with tapentadol IR compared with oxycodone IR at the lowest dose of tapentadol (50 mg) (RR 0.62; 95% CI, 0.51 to 0.76, p<0.01).[16] However, no difference for any other dose level was found: 75 mg (RR 0.93; 95% CI, 0.71 to 1.21, p=0.58), 100 mg (RR 1.10; 95% CI, 0.89 to 1.36, p=0.36), and titrated dose group (RR 1.13; 95% CI, 0.76 to 1.67; p=0.56).[16] Heterogeneity ranged from none-to-moderate for the dose groups (I^2 = 0% to 36%).[16]

In the qualitative analysis of studies evaluating tapentadol IR versus morphine IR, the analgesic effect (mean total pain relief over 8 hours) after dental surgery (n=400) was greater with tapentadol IR 200 mg versus morphine IR 60 mg, but the tapentadol 100 mg dose was less effective than the morphine 60 mg dose.[16] In an abdominal hysterectomy trial (n=850), the sum pain intensity difference measured at 24 hours was similar between tapentadol (50, 75 and 100 mg) and morphine IR 20 mg.[16] In a bunionectomy trial (n=291), the sum pain intensity difference measured at 48 hours was similar between tapentadol IR 75 mg and morphine 30 mg.[16] In both trials, medications were administered every 4 to 6 hours for 72 hours after surgery.[16]

After cardiac surgery, tapentadol IR 50 mg (n=30) was associated with greater improved mean pain score on a Visual Analogue Scale 3 hours post-dose than tramadol 100 mg (n=30).[16] Tapentadol was also associated with a lower incidence of post-operative nausea and vomiting than tramadol.[16] Both drugs were administered three times daily.[16] In patients with osteoarthritic knee pain, no difference was found between tapentadol IR 50 mg (n=50) and tramadol 50 mg (n=50) when administered twice daily for 1 week.[16]

In a retrospective cohort of hospitalized patients who received tapentadol IR (n=1,858) or oxycodone IR (n=5,574), patients were less likely to receive antinausea treatment if they received tapentadol versus oxycodone (30% vs. 34%; p=0.001).[16] Patient who received tapentadol were also less likely to receive drug

treatment for constipation (28% vs. 34%; p<0.001).[16] No other statistics for these comparisons (i.e., 95% CI) were provided in the review of this retrospective study.[16]

The investigators concluded that tapentadol IR is not superior to oxycodone IR in managing acute pain and lower doses of tapentadol IR (e.g., 50 mg) may be less effective than oxycodone IR.[16] However, tapentadol IR may have better tolerability in terms of adverse gastrointestinal effects than oxycodone.[16]

Cochrane Collaboration: Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (2020)

Sickle cell disease (SCD) is a group of inherited disorders of hemoglobin (Hb) structure and is characterized by distorted, sickle-shaped red blood cells. It is estimated that between 5% and 7% of the world's population are carriers of the mutant Hb gene, and SCD is the most commonly inherited blood disorder.[17] Signs and symptoms of SCD are attributed to either hemolysis (premature red cell destruction) or vaso-occlusion (obstruction of blood flow, the most common manifestation).[17] Vaso-occlusion can lead to an acute, painful crisis. The pain experienced during a sickle cell crisis is both acute and recurrent. Key pharmacological treatments for vaso-occlusive crisis include opioid analgesics, non-opioid analgesics, and combinations of drugs.

The objective of this systematic review was to assess the analgesic efficacy and adverse events of pharmacological interventions to treat acute painful sickle cell vaso-occlusive crises in adults, in any setting.[17] These included (but were not limited to) opioid and non-opioid analgesics. Included studies were randomized, controlled, double-blind trials of pharmacological interventions, of any dose and by any route, compared to placebo or any active comparator, for the treatment of painful sickle cell vaso-occlusive virus in adults.[17]

The primary outcomes were patient-reported pain relief of 50% or greater, or 30% or greater; and Patient Global Impression of Change (PGIC) of *very much* improved, or *much* improved.[17] Secondary outcomes included adverse events, serious adverse events, and withdrawals due to adverse events.[17]

The review included 9 studies with data for 638 vaso-occlusive crisis events and 594 patients aged 17 to 42 years with SCD presenting to a hospital emergency department in a painful vaso-occlusive crisis.[17] One study compared an opioid with placebo, two studies compared an opioid with an active comparator, and one study compared a combination of 3 drugs with a combination of 4 drugs.[17] Risk of bias across the 9 studies varied. Studies were primarily at an unclear risk of selection, performance, and detection bias.[17]

In studies that compared opioids with placebo, no data were reported regarding patient-reported pain relief of 50% or greater, or 30% or greater, PGIC, or adverse events (any adverse event, serious adverse events, and withdrawals due to adverse events).[17]

In studies that compared opioids (morphine) with an active comparator (acetaminophen or butorphanol), no data were reported regarding patient-reported pain relief of 50% or greater, or 30% or greater.[17] The results were uncertain regarding patients who reported *very much* improved by PGIC (33% of the opioids group versus 19% of the placebo group).[17] No data were reported regarding PGIC of *much* improved. Very low-quality, uncertain results suggested similar rates of adverse events across both the opioids group (9/66 adverse events, and 0/66 serious adverse events) and the active comparator group (7/64 adverse events, 0/66 serious adverse events).[17] No data were reported regarding withdrawal due to adverse events.[17]

The researchers concluded that the available evidence regarding the efficacy or harm from pharmacological interventions used to treat pain related to sickle cell vaso-occlusive crises in adults is very uncertain.[17] An emphasis was also placed for more high quality research in pain management for SCD, as well as the establishment of suitable registries which record interventions and outcomes for these patients.[17]

A Systematic Review of the Recommendations for the Prescription of Opioids at Discharge After Abdominopelvic Surgery (2020)

The research on prescription of opioids at discharge after abdominopelvic surgery shows substantial variation.[18] A lack of guidance for surgeons has been cited as a major factor contributing to the variation of current prescribing practices.[18] A systematic review was conducted of existing recommendations on the prescription of opioids at discharge, the appropriate disposal of opioids, and the prevention of chronic postsurgical opioid use after abdominopelvic surgery.[18] Specifically, the study aimed to systematically review existing recommendations within the following 3 areas of focus: (1) the prescription of opioids at discharge, (2) the appropriate disposal of opioids, and (3) the prevention of chronic postsurgical opioid use after abdominopelvic surgery.[18]

Identified among the 41 included documents were 98 recommended interventions for the prescription of opioids at discharge, 8 interventions for the disposal of opioids, and 8 interventions for the prevention of chronic post-operative opioid use.[18] Of the 41 documents, 30 originated from North America, and 25 were clinical practice guidelines or original studies.[18] For the prescription of opioids at discharge, 25 interventions were identified that provided general guidance, 11 co-interventions, and 62 prescription regimens after 21 specific abdominopelvic surgical procedures.[18] Seventeen documents provided recommendations that specifically targeted pain management after abdominopelvic procedures.[18] The quality of the clinical practice guidelines scored moderate or high based on scope and purpose, stakeholder involvement, rigor of development, and editorial independence.[18]

Fourteen publishing bodies recommended a multimodal approach to pain management, and only 3 documents provided an associated level of evidence.[18] Ten documents recommended that clinicians ensure that opioids are appropriately indicated.[18] Although some recommendations acknowledged that opioids are generally required for the treatment of moderate to severe pain immediately after surgical procedures, several documents recommended that the need for opioid treatment should be reassessed at discharge, and the prescription should be based on in-hospital opioid use.[18] Five documents recommended caution when prescribing opioids to the following special patient populations: those with concurrent alcohol, benzodiazepines, or other drug use; kidney or liver impairment; delirium, dementia, or fall risk and psychiatric comorbidities; existing opioid prescription; respiratory insufficiency or sleep apnea, concerns with safe driving, advanced age, or breastfeeding.[18] Specifically, concurrent opioid use should be avoided in individuals performing safety-sensitive jobs or jobs involving high levels of cognitive function and judgment.[18]

Recommendations regarding the type of opioid were generally consistent in that the least potent opioid type should be prescribed, but few documents provided guidance as to specific agents to use.[18] One guideline recommended oxycodone as the preferred option for acute pain treatments, but another suggested that morphine sulfate be used as the gold standard.[18] Regardless of document type, oxycodone was the most commonly recommended type of opioid.[18] Nonetheless, it was recommended that a morphine equivalence charge be utilized when choosing opioids.[18] Regarding opioid formulations, all documents that addressed this recommended immediate-release opioids and recommended against long-acting opioids.[18] The dose of opioid should be the lowest possible, and daily doses should not exceed 30-50 morphine milligram equivalents (MME).[18] The duration of the opioid prescription should be based on the expected length of pain, and clinicians should generally prescribe opioids for less than 3 days according to some documents, or 3 to 5 days according to other documents.[18]

The search identified 11 co-interventions relevant to the prescription of opioids at discharge after abdominopelvic surgery, but only 2 interventions (patient education and comprehensive patient assessment) were supported by a recommendation strength and level of evidence.[18] Patient education was recommended in 21 of the 43 documents.[18] Patient education and the plan for taper and discontinuation of the opioid received strong recommendations but are based on low quality evidence.[18]

The investigators concluded that current guidance for the prescription of opioids at discharge after abdominopelvic surgery is heterogeneous and rarely supported by evidence, and more research is needed to guide the development recommendations.[18]

Excluded Systematic Reviews:
After review, 7 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational, network meta-analysis),[19-23] comparator (e.g., no control or placebo-controlled),[24] focus on injectable interventions,[25] or outcome studied (e.g., non-clinical, non-funded condition under OHP).[26]

New Guidelines:
The American College of Rheumatology and the Arthritis Foundation
The American College of Rheumatology and the Arthritis Foundation developed a guideline for the management of osteoarthritis (OA) of the hip, knee and hand using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop recommendations.[27] The guideline was based on a systematic review of RCTs performed by members of the guideline task force.[27] Systematic reviews of observational studies were included if it was determined they added critical information for the formulation of a recommendation (e.g., adverse events that may not be captured in a short-duration RCT).[27] Recommendations in the guideline were influenced by limitations of any informing RCTs, including publication bias, inadequate blinding, and inadequate control groups.[27] Duration of RCTs were also considered a limitation since shorter-duration studies may not provide adequate prognostic information for a slowly progressive condition like OA.[27] Using GRADE, each recommendation was either in favor of or against the proposed intervention and either strong or conditional.[27] Strong recommendations were made when there was compelling evidence of efficacy and that benefits of therapy clearly outweighed harms and burdens.[27] Conditional recommendations were made when the quality of evidence was low or very low or the balance of benefits versus harms and burdens was sufficiently close that shared decision-making between the patient and clinician would be particularly important.[27] The strength of recommendation was based on a 70% consensus among members of the task force.[27]

Most of the evidence provided indirect (did not specifically address the PICO question as written) but included several comprehensive, non-pharmacological strategies.[27] Pharmacologic management for OA of the hand, knee and hip include topical, oral, and intraarticular treatments.[27] Non-opioid treatments strongly recommended in the guideline included oral nonsteroidal anti-inflammatory drugs (NSAIDs) for hand, knee and hip OA; topical NSAIDs for knee OA; intraarticular glucocorticoid injection for hip and knee OA; and ultrasound-guided intraarticular glucocorticoid injection for hip OA.[27] Conditional recommendations for all 3 OA conditions were made for acetaminophen, duloxetine, and tramadol.[27] Of importance to this review, opioids (excluding tramadol) received a conditional recommendation against use in hand, hip and knee OA.[27] The guideline noted very modest benefits of long-term opioid therapy for treatment of OA and high risk of toxicity and dependence.[27] No comparison between opioid formulations were made in the guideline.[27]

The American College of Physicians and American Academy of Family Physicians
The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) developed a guideline for nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults.[28] The guideline did not address non-invasive treatment of low back pain. The guideline was based on 2 systematic reviews: a network meta-analysis on the comparative efficacy and safety of nonpharmacologic and pharmacologic treatments for acute musculoskeletal injuries and a systematic review on the predictors of long-term opioid use.[28] Both reviews that informed this guideline were performed by an evidence review team at McMaster University and funded by the National Safety Council, which did not have a role in the development, review, or approval of this guideline or the 2 systematic reviews.[28] The network meta-analysis included 207 trials comprised of 32,959 patients (median age 34 years) with a range of causes of acute musculoskeletal pain (mixed musculoskeletal injury; sprains; whiplash; strains; and nonsurgical fractures or contusions).[28]

They selected studies published up to January 2020 that assessed adults aged 18 years or older with acute musculoskeletal pain (excluding treatment of low back pain) in the outpatient setting.[28] Acute pain was defined as lasting less than 4 weeks.[28] The meta-analysis evaluated the following outcomes: pain relief; physical function; symptom relief; treatment satisfaction; and gastrointestinal (GI) and neurologic adverse events.[28] Pain relief and function were reported as mean score differences on a 10-cm visual analogue scale (VAS) using a minimally important difference of 1 cm, whereas symptom relief, treatment satisfaction, and adverse events were reported as dichotomous outcomes.[28] Using GRADE methodology, the guideline task force based recommendations on an assessment of the benefits and harms of the treatment and consideration of costs and patient values and preferences.[28]

Evidence presented in the guideline from the two systematic reviews specific to opioids is summarized as follows:

Of the pharmacologic interventions that evaluated pain relief at 2 hours post-dose, there was evidence from one study which showed that on a 10-cm VAS, acetaminophen plus opioids reduced pain at less than 2 hours (Weighted Mean Difference [WMD] -0.50 cm; 95% CI, -1.00 to -0.01 cm), although the effect was small and not clinically meaningful.[28] For context, other interventions also provided moderate quality evidence for pain reduction at less than 2 hours versus placebo: acetaminophen alone (WMD -1.03 cm; 95% CI, -1.82 to -0.24 cm); acetaminophen plus oral diclofenac (WMD -1.11 cm; 95% CI, -2.00 to -0.21 cm); oral NSAIDs (WMD -0.93 cm; 95% CI, -1.49 to -0.37 cm); and topical NSAIDs (WMD -1.02 cm; 95% CI, -1.64 to -0.39 cm).[28] Low-quality evidence from a small, single-center study showed that a single dose of buccal fentanyl also reduced pain at less than 2 hours compared with placebo (WMD -3.52 cm; 95% CI, -4.99 to -2.04 cm).[28] Moderate-certainty evidence indicated that neither the combination of acetaminophen plus ibuprofen plus oxycodone nor tramadol alone showed statistically significant pain reduction at less than 2 hours compared with placebo.[28]

Of the pharmacologic interventions that evaluated pain relief at 1 to 7 days, there was evidence which showed that on a 10-cm VAS, acetaminophen plus opioids reduced pain at 1 to 7 days (WMD -1.71 cm; 95% CI, -2.97 to -0.46 cm).[28] For context, other interventions also provided moderate quality evidence for pain reduction at 1 to 7 days versus placebo: acetaminophen alone (WMD -1.07 cm; 95% CI, -1.89 to -0.24 cm); oral NSAIDs (WMD -0.99 cm; 95% CI, -1.46 to -0.52 cm); and topical NSAIDs (WMD -1.08 cm; 95% CI, -1.40 to -0.75 cm).[28]

Of the pharmacologic interventions that evaluated physical function, there was insufficient evidence to determine the impact of opioids.[28]

Of the pharmacologic interventions that evaluated symptom relief, acetaminophen plus opioids increased likelihood of symptom relief compared with placebo (OR 1.44; 95% CI, 1.03 to 2.03).[28] For context, moderate-certainty evidence showed that acetaminophen plus oral diclofenac (OR 3.72; 95% CI, 1.02 to 13.52), oral NSAIDs (OR 3.10; 95% CI, 1.39 to 6.91), and topical NSAIDs (OR 6.39; 95% CI, 3.48 to 11.75) also improved symptom relief.[28]

Forty-five studies comprised of 7070 patients reported GI adverse events, which included abdominal pain or cramps, bleeding, constipation, diarrhea, distension, dry mouth, dyspepsia, epigastric pain or discomfort, flatulence, gastritis, gastroenteritis, heartburn, indigestion, nausea, salivation, ulcer, and vomiting.[28] Buccal fentanyl (OR 59.38; 95% CI, 6.21 to 567.71), acetaminophen plus opioids (OR 5.63; 95% CI, 2.84 to 11.16), and oral NSAIDs (OR 1.77; 95% CI, 1.33 to 2.35) increased risk for GI adverse events based on moderate-quality evidence.[28]

Thirty-eight studies comprised of 6245 patients reported neurologic adverse events, which included agitation, anxiety, blurred vision, confusion, dizziness, drowsiness, dysphoria, fatigue, headache, insomnia, lightheadedness, malaise, nerve palsies, nervousness, paresthesia sedation, sleepiness, somnolence, tiredness, and vertigo.[28] Acetaminophen plus opioids (OR 3.53; 95% CI, 1.92 to 6.49) increased neurologic adverse events more than placebo based on high-

quality evidence.[28] An increase in neurologic adverse events was also seen with tramadol (OR 6.72; 95% CI, 1.24 to 36.39) and buccal fentanyl (OR 5.73; 95% CI, 1.20 to 27.47) based on moderate-quality evidence.[28]

The other separate systematic review evaluated predictors of prolonged opioid use after a prescription to treat acute musculoskeletal pain.[28] There was moderate-quality evidence for an association between prolonged opioid use and greater physical comorbidity (absolute risk increase [ARI], 0.9%; 95% CI, 0.1% to 1.7%), age (ARI for every 10-year increase, 1.1%; 95% CI, 0.7% to 1.5%), and past or present substance use disorder (ARI, 10.5%; 95% CI, 4.2% to 19.8%).[28] There was low-quality evidence from studies that could not be pooled which showed that prolonged opioid use was associated with prescriptions lasting more than 7 days (ARI ranged from 2% to 9%) and higher morphine milligram equivalents per day (ARI ranged from 2% to 13%).[28]

The ACP and AAFP made the following opioid-specific recommendation based on the evidence related to opioids[28]:

RECOMMENDATION: ACP and AAFP suggest *against* clinicians treating patients with acute pain from non–low back, musculoskeletal injuries with opioids, including tramadol (Grade: conditional recommendation; low-certainty evidence).
RATIONALE: Opioid interventions are associated with large increases in the risk for neurologic and GI adverse events. Evidence shows a relationship between prescriptions lasting longer than 7 days and prolonged use of opioids, as well as an associated between long-term addiction and overdose.

<u>The Department of Veterans Affairs and Department of Defense:</u>
The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-based Practice Work Group published a clinical practice guideline in 2020 to provide a framework for primary care providers to evaluate and treat patients with headache and thereby improve clinical outcomes.[29] In broad terms, headaches can be divided into two types: primary headache disorders and secondary headache disorders.[29] Primary headache disorders refer to a set of headaches that are idiopathic, recurrent, and stereotyped, without underlying secondary causes.[29] These include tension-type headache, migraine and cluster-type headache.[29] Secondary headaches can be attributed to an identifiable underlying cause that may be structural, pharmacologic, vascular, or related to a systemic illness or disorder of homeostasis.[29] The GRADE system was used to assess the quality of the evidence base and to assign a strength for each recommendation.[29] The relative strength of each recommendation was categorized as "Strong" or "Weak." A strong recommendation indicated a high confidence in the quality of the evidence, a clear difference in magnitude between the benefits and harms of the intervention, similar patient or provider values and preferences, and understood influence of other implications (e.g., resource use, feasibility).[29] A weak recommendation indicated less confidence after the assessment across these domains and belief from the work group that additional evidence may change the recommendation.[29]

In general, opioid therapy was not included or mentioned in the 42 recommendations made in the guideline on the management of primary and secondary headache disorders.[29] One exception was a weak recommendation based on low quality evidence for the use of triptans *instead of* opioids or nonopioid analgesics to lower the risk of medication overuse headache for the acute treatment of migraine.[29] This recommendation was based on a systematic review of observational studies that found that triptans are associated with a statistically significantly lower incidence of medication overuse headache compared to opioids. In general, opioids are not recommended for the management of migraine.[29]

New Formulations:
PROLATE (oxycodone/acetaminophen) [C-II] was approved by the FDA in January 2020. It is another short-acting oxycodone product combined with 300 mg acetaminophen in a tablet formulation.[30] PROLATE is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[30] No published clinical trials assessing clinical outcomes were identified. The FDA boxed warnings for oxycodone products apply to PROLATE:

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS.[30]

QDOLO (tramadol) [C-IV] was approved by the FDA in September 2020. It is a short-acting tramadol 5 mg/mL oral solution product.[31] QDOLO is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[31] No published clinical trials assessing clinical outcomes were identified. The FDA boxed warnings for tramadol products apply to QDOLO:

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, and MISUSE; RISK EVALUATION and MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL and OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS.[31]

New FDA Safety Alerts:
None identified.

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Appendix 1: Current Preferred Drug List

Long-Acting Opioids

Generic	Brand	Route	Form	PDL
fentanyl	DURAGESIC	TRANSDERM	PATCH TD72	Y
fentanyl	FENTANYL	TRANSDERM	PATCH TD72	Y
fentanyl	FENTANYL	TRANSDERM	PATCH TD72	Y
morphine sulfate	MORPHINE SULFATE CR	ORAL	TABLET ER	Y
morphine sulfate	MORPHINE SULFATE ER	ORAL	TABLET ER	Y
morphine sulfate	MORPHINE SULFATE ER	ORAL	TABLET ER	Y
morphine sulfate	MS CONTIN	ORAL	TABLET ER	Y
morphine sulfate	MS CONTIN	ORAL	TABLET ER	Y
buprenorphine	BUPRENORPHINE	TRANSDERM	PATCH TDWK	N
buprenorphine	BUPRENORPHINE	TRANSDERM	PATCH TDWK	N
buprenorphine	BUTRANS	TRANSDERM	PATCH TDWK	N
buprenorphine	BUTRANS	TRANSDERM	PATCH TDWK	N
buprenorphine HCl	BELBUCA	BUCCAL	FILM	N
fentanyl	FENTANYL	TRANSDERM	PATCH TD72	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	ORAL	CAP ER 12H	N
hydrocodone bitartrate	HYSINGLA ER	ORAL	TAB ER 24H	N
hydrocodone bitartrate	ZOHYDRO ER	ORAL	CAP ER 12H	N
hydromorphone HCl	EXALGO	ORAL	TAB ER 24H	N
hydromorphone HCl	HYDROMORPHONE ER	ORAL	TAB ER 24H	N
levorphanol tartrate	LEVORPHANOL TARTRATE	ORAL	TABLET	N
methadone HCl	DISKETS	ORAL	TABLET SOL	N
methadone HCl	METHADONE HCL	ORAL	ORAL CONC	N
methadone HCl	METHADONE HCL	ORAL	SOLUTION	N
methadone HCl	METHADONE HCL	ORAL	SOLUTION	N
methadone HCl	METHADONE HCL	ORAL	TABLET	N
methadone HCl	METHADONE HCL	ORAL	TABLET	N
methadone HCl	METHADONE HCL	ORAL	TABLET SOL	N
methadone HCl	METHADONE INTENSOL	ORAL	ORAL CONC	N
methadone HCl	METHADOSE	ORAL	ORAL CONC	N
methadone HCl	METHADOSE	ORAL	TABLET	N
methadone HCl	METHADOSE	ORAL	TABLET SOL	N
morphine sulfate	ARYMO ER	ORAL	TAB PO ER	N
morphine sulfate	KADIAN	ORAL	CAP ER PEL	N
morphine sulfate	KADIAN	ORAL	CAP ER PEL	N
morphine sulfate	MORPHABOND ER	ORAL	TAB ER 12H	N

morphine sulfate	MORPHINE SULFATE ER	ORAL	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	ORAL	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	ORAL	CPMP 24HR	N
oxycodone HCl	OXYCODONE HCL ER	ORAL	TAB ER 12H	N
oxycodone HCl	OXYCODONE HCL ER	ORAL	TAB ER 12H	N
oxycodone HCl	OXYCONTIN	ORAL	TAB ER 12H	N
oxycodone HCl	OXYCONTIN	ORAL	TAB ER 12H	N
oxycodone myristate	XTAMPZA ER	ORAL	CAP SPR 12	N
oxycodone myristate	XTAMPZA ER	ORAL	CAP SPR 12	N
oxymorphone HCl	OXYMORPHONE HCL ER	ORAL	TAB ER 12H	N
oxymorphone HCl	OXYMORPHONE HCL ER	ORAL	TAB ER 12H	N
tapentadol HCl	NUCYNTA ER	ORAL	TAB ER 12H	N
tramadol HCl	CONZIP	ORAL	CPBP 17-83	N
tramadol HCl	CONZIP	ORAL	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	ORAL	CPBP 17-83	N
tramadol HCl	TRAMADOL HCL ER	ORAL	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	ORAL	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	ORAL	TAB ER 24H	N
tramadol HCl	TRAMADOL HCL ER	ORAL	TAB ER 24H	N
tramadol HCl	TRAMADOL HCL ER	ORAL	TBMP 24HR	N
tramadol HCl	TRAMADOL HCL ER	ORAL	TBMP 24HR	N
tramadol HCl	ULTRAM ER	ORAL	TAB ER 24H	N

Short-Acting Opioids

Generic	Brand	Route	Form	PDL
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ORAL	ELIXIR	Y
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ORAL	ELIXIR	Y
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ORAL	TABLET	Y
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ORAL	TABLET	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	ORAL	SOLUTION	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	ORAL	SOLUTION	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	ORAL	TABLET	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	ORAL	TABLET	Y
acetaminophen with codeine	TYLENOL W/CODEINE NO.3	ORAL	TABLET	Y
acetaminophen with codeine	TYLENOL W/CODEINE NO.4	ORAL	TABLET	Y
acetaminophen with codeine	TYLENOL-CODEINE NO.3	ORAL	TABLET	Y
butorphanol tartrate	BUTORPHANOL TARTRATE	NASAL	SPRAY	Y
butorphanol tartrate	BUTORPHANOL TARTRATE	NASAL	SPRAY	Y
codeine sulfate	CODEINE SULFATE	ORAL	TABLET	Y

hydrocodone/acetaminophen	ANEXSIA	ORAL	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ORAL	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ORAL	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE/ACETAMINOPHEN	ORAL	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	SOLUTION	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	SOLUTION	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORCET	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORCET 10/650	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORCET HD	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORCET PLUS	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORCET PLUS	ORAL	TABLET	Y
hydrocodone/acetaminophen	LORTAB	ORAL	SOLUTION	Y
hydrocodone/acetaminophen	LORTAB	ORAL	TABLET	Y
hydrocodone/acetaminophen	NORCO	ORAL	TABLET	Y
hydrocodone/acetaminophen	NORCO	ORAL	TABLET	Y
hydrocodone/acetaminophen	VICODIN	ORAL	TABLET	Y
hydrocodone/acetaminophen	VICODIN ES	ORAL	TABLET	Y
hydrocodone/acetaminophen	VICODIN HP	ORAL	TABLET	Y
hydromorphone HCl	DILAUDID	ORAL	TABLET	Y
hydromorphone HCl	DILAUDID	ORAL	TABLET	Y
hydromorphone HCl	DILAUDID	RECTAL	SUPP.RECT	Y
hydromorphone HCl	DILAUDID STRIP PACKS	ORAL	TABLET	Y
hydromorphone HCl	HYDROMORPHONE HCL	ORAL	TABLET	Y
hydromorphone HCl	HYDROMORPHONE HCL	ORAL	TABLET	Y
hydromorphone HCl	HYDROMORPHONE HCL	RECTAL	SUPP.RECT	Y
morphine sulfate	MORPHINE SULFATE	ORAL	SOLUTION	Y
morphine sulfate	MORPHINE SULFATE	ORAL	SOLUTION	Y
morphine sulfate	MORPHINE SULFATE	ORAL	TABLET	Y
morphine sulfate	MORPHINE SULFATE	ORAL	TABLET	Y
morphine sulfate	MORPHINE SULFATE	RECTAL	SUPP.RECT	Y
opium/belladonna alkaloids	B & O SUPPRETTES NO.15-A	RECTAL	SUPP.RECT	Y
opium/belladonna alkaloids	B & O SUPPRETTES NO.16-A	RECTAL	SUPP.RECT	Y
opium/belladonna alkaloids	BELLADONNA & OPIUM	RECTAL	SUPP.RECT	Y
opium/belladonna alkaloids	BELLADONNA-OPIUM	RECTAL	SUPP.RECT	Y
oxycodone HCl	OXYCODONE HCL	ORAL	SOLUTION	Y
oxycodone HCl	OXYCODONE HCL	ORAL	TABLET	Y
oxycodone HCl	OXYCODONE HCL	ORAL	TABLET	Y
oxycodone HCl	ROXICODONE	ORAL	TABLET	Y

oxycodone HCl/acetaminophen	ENDOCET	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	ENDOCET	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	NALOCET	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE HCL-ACETAMINOPHEN	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	ORAL	CAPSULE	Y
oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	PERCOCET	ORAL	TABLET	Y
oxycodone HCl/acetaminophen	PERCOCET	ORAL	TABLET	Y
tramadol HCl	TRAMADOL HCL	ORAL	TABLET	Y
tramadol HCl	TRAMADOL HCL	ORAL	TABLET	Y
tramadol HCl	ULTRAM	ORAL	TABLET	Y
tramadol HCl	ULTRAM	ORAL	TABLET	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	ORAL	SOLUTION	N
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	ORAL	CAPSULE	N
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	ORAL	TABLET	N
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	ORAL	TABLET	N
acetaminophen/caff/dihydrocod	DVORAH	ORAL	TABLET	N
acetaminophen/caff/dihydrocod	PANLOR	ORAL	TABLET	N
acetaminophen/caff/dihydrocod	TREZIX	ORAL	CAPSULE	N
aspirin/caffein/dihydrocodeine	SYNALGOS-DC	ORAL	CAPSULE	N
aspirin/caffeine/dihydrocodein	SYNALGOS-DC	ORAL	CAPSULE	N
aspirin/codeine phosphate	ASPIRIN W/CODEINE	ORAL	TABLET	N
aspirin/codeine phosphate	ASPIRIN W/CODEINE	ORAL	TABLET	N
benzhydrocodone/acetaminophen	APADAZ	ORAL	TABLET	N
benzhydrocodone/acetaminophen	BENZHYDROCODONE-ACETAMINOPHEN	ORAL	TABLET	N
butalbit/acetamin/caff/codeine	BUTALB-ACETAMINOPH-CAFF-CODEIN	ORAL	CAPSULE	N
butalbit/acetamin/caff/codeine	BUTALB-CAFF-ACETAMINOPH-CODEIN	ORAL	CAPSULE	N
butalbit/acetamin/caff/codeine	BUTALB-CAFF-ACETAMINOPH-CODEIN	ORAL	CAPSULE	N
cod/ASA/salicylmd/acetamin/caf	RID-A-PAIN W/CODEINE	ORAL	TABLET	N
codeine/butalbital/ASA/caffein	ASA-BUTALB-CAFFEINE-CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	ASA-BUTALB-CAFFEINE-CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	ASCOMP WITH CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	BUTALBITAL COMPOUND W/CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	BUTALBITAL COMPOUND-CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	BUTALBITAL COMPOUND-CODEINE	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	FIORINAL W/CODEINE #3	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	FIORINAL WITH CODEINE #3	ORAL	CAPSULE	N
codeine/butalbital/ASA/caffein	FIORINAL WITH CODEINE #3	ORAL	CAPSULE	N

fentanyl	SUBSYS	SUBLINGUAL	SPRAY	N
fentanyl citrate	ABSTRAL	SUBLINGUAL	TAB SUBL	N
fentanyl citrate	ACTIQ	BUCCAL	LOZENGE HD	N
fentanyl citrate	ACTIQ	BUCCAL	LOZENGE HD	N
fentanyl citrate	FENTANYL CITRATE	BUCCAL	LOZENGE HD	N
fentanyl citrate	FENTANYL CITRATE	BUCCAL	LOZENGE HD	N
fentanyl citrate	FENTANYL CITRATE	BUCCAL	TABLET EFF	N
fentanyl citrate	FENTORA	BUCCAL	TABLET EFF	N
fentanyl citrate	LAZANDA	NASAL	SPRAY/PUMP	N
hydrocodone bitartrate/aspirin	LORTAB ASA	ORAL	TABLET	N
hydrocodone/acetaminophen	DOLAGESIC	ORAL	CAPSULE	N
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ORAL	ELIXIR	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	TABLET	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	ORAL	TABLET	N
hydrocodone/acetaminophen	LORCET HD	ORAL	CAPSULE	N
hydrocodone/acetaminophen	VERDROCET	ORAL	TABLET	N
hydrocodone/ibuprofen	HYDROCODONE BIT-IBUPROFEN	ORAL	TABLET	N
hydrocodone/ibuprofen	HYDROCODONE-IBUPROFEN	ORAL	TABLET	N
hydrocodone/ibuprofen	HYDROCODONE-IBUPROFEN	ORAL	TABLET	N
hydrocodone/ibuprofen	VICOPROFEN	ORAL	TABLET	N
hydrocodone/ibuprofen	XYLON 10	ORAL	TABLET	N
hydromorphone HCl	DILAUDID	ORAL	LIQUID	N
hydromorphone HCl	DILAUDID-5	ORAL	LIQUID	N
hydromorphone HCl	HYDROMORPHONE HCL	ORAL	LIQUID	N
ibuprofen/oxycodone HCl	OXYCODONE HCL-IBUPROFEN	ORAL	TABLET	N
meperidine HCl	MEPERIDINE HCL	ORAL	SOLUTION	N
meperidine HCl	MEPERIDINE HCL	ORAL	TABLET	N
meperidine HCl	MEPERIDINE HCL	ORAL	TABLET	N
morphine sulfate	MORPHINE SULFATE	ORAL	SYRINGE	N
morphine sulfate	MORPHINE SULFATE	ORAL	SYRINGE	N
oxycodone HCl	OXAYDO	ORAL	TABLET ORL	N
oxycodone HCl	OXAYDO	ORAL	TABLET ORL	N
oxycodone HCl	OXYCODONE HCL	ORAL	CAPSULE	N
oxycodone HCl	OXYCODONE HCL	ORAL	CAPSULE	N
oxycodone HCl	OXYCODONE HCL	ORAL	ORAL CONC	N
oxycodone HCl	OXYCODONE HCL	ORAL	SYRINGE	N
oxycodone HCl	ROXYBOND	ORAL	TABLET ORL	N
oxycodone HCl/acetaminophen	PRIMLEV	ORAL	TABLET	N
oxycodone HCl/acetaminophen	PROLATE	ORAL	TABLET	N
oxycodone HCl/acetaminophen	ROXICET	ORAL	TABLET	N

oxycodone HCl/aspirin	OXYCODONE HCL-ASPIRIN	ORAL	TABLET	N
oxymorphone HCl	NUMORPHAN	RECTAL	SUPP.RECT	N
oxymorphone HCl	OPANA	ORAL	TABLET	N
oxymorphone HCl	OXYMORPHONE HCL	ORAL	TABLET	N
oxymorphone HCl	OXYMORPHONE HCL	ORAL	TABLET	N
pentazocine HCl/naloxone HCl	PENTAZOCINE-NALOXONE HCL	ORAL	TABLET	N
pentazocine HCl/naloxone HCl	PENTAZOCINE-NALOXONE HCL	ORAL	TABLET	N
pentazocine HCl/naloxone HCl	TALWIN NX	ORAL	TABLET	N
propoxyphene HCl	PROPOXYPHENE HCL	ORAL	CAPSULE	N
propoxyphene HCl/acetaminophen	PROPOXYPHENE HCL W/APAP	ORAL	TABLET	N
propoxyphene nap/acetaminophen	DARVOCET-N 100	ORAL	TABLET	N
propoxyphene nap/acetaminophen	PROPOXACET-N 100	ORAL	TABLET	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE W/APAP	ORAL	TABLET	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE W/APAP	ORAL	TABLET	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE-APAP	ORAL	TABLET	N
propoxyphene/aspirin/caffeine	PROPOXYPHENE HCL COMPOUND	ORAL	CAPSULE	N
sufentanil citrate	DSUVIA	SUBLINGUAL	TAB IN APP	N
tapentadol HCl	NUCYNTA	ORAL	TABLET	N
tapentadol HCl	NUCYNTA	ORAL	TABLET	N
tramadol HCl	TRAMADOL HCL	ORAL	TABLET	N
tramadol HCl/acetaminophen	TRAMADOL HCL-ACETAMINOPHEN	ORAL	TABLET	N
tramadol HCl/acetaminophen	TRAMADOL HCL-ACETAMINOPHEN	ORAL	TABLET	N
tramadol HCl/acetaminophen	ULTRACET	ORAL	TABLET	N
tramadol HCl/acetaminophen	ULTRACET	ORAL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 213 citations of randomized controlled trials were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study setting (e.g., inpatient, intraoperative), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Two head-to-head trials were identified but involved formulations not approved by the FDA.[32,33]

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL, 1946 to January 15, 2021

1 fentanyl.mp. or exp Fentanyl/ 25448
2 morphine.mp. or exp Morphine/ 59933
3 exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/ or buprenorphine.mp. 8211
4 hydrocodone.mp. or exp Hydrocodone/ 1320
5 hydromorphone.mp. or exp Hydromorphone/ 2217
6 levorphanol.mp. or exp Levorphanol/ 847
7 methadone.mp. or exp Methadone/ 17326
8 oxycodone.mp. or exp Oxycodone/ 4316
9 oxymorphone.mp. or exp Oxymorphone/ 799
10 tapentadol.mp. or exp Tapentadol/ 563
11 tramadol.mp. or exp Tramadol/ 5774
12 codeine.mp. or exp Codeine/ 9611
13 butorphanol.mp. or exp Butorphanol/ 1681
14 exp Opium/ or exp Atropa belladonna/ 2927
15 benzhydrocodone.mp. 8
16 dihydrocodeine.mp. 499
17 meperidine.mp. or exp Meperidine/ 6909
18 pentazocine.mp. or exp Pentazocine/ 3034
19 propoxyphene.mp. or exp Dextropropoxyphene/ 1751
20 sufentanil.mp. or exp Sufentanil/ 3064
21 exp Analgesics, Opioid/ 118509
22 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/ 151846
23 limit 22 to (yr="2020 -Current" and (meta-analysis or "systematic review")) 122
23 limit 22 to (yr="2020 -Current" and randomized controlled trial) 213
23 limit 22 to (yr="2020 -Current" and practice guideline) 8

Appendix 4: Key Inclusion Criteria

Population	Adult or Pediatric Patients with acute or chronic pain
Intervention	Opioid Approved by U.S. Food and Drug Administration
Comparator	Opioid or Non-opioid Analgesics
Outcomes	Reduction in Pain or Change in Functioning
Timing	Multi-dose Regimen
Setting	Outpatient; Post-operative and Emergency Department Considered

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:

Initial: 90 days (except 12 months for end-of-life, sickle-cell disease, severe burn, or cancer-related pain)
Renewal: Up to 6 months

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.

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. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.
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 Frequency Limits per FDA-approved Labeling.

Drug Product	Quantity Limit
BELBUCA	2 doses/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hr

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
MS CONTIN	3 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day

Drug Product	Quantity Limit
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on any opioid treatment for >6 weeks (long-term, chronic treatment)?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #3

3. 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, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
4. Is the requested medication a preferred agent?	**Yes:** Go to #6	**No:** Go to #5
5. 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 #6
6. 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 #7
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 prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past month that opioid prescribing is appropriate?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. 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 #11
11. 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:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
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 3 months 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.

Renewal Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**
3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #5 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness

5. 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 1 month that opioid prescribing is appropriate?	**Yes:** Go to #6	**No:** Pass to RPh. Deny. Medical appropriateness
6. 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 #7	**No:** Pass to RPh. Deny. Medical appropriateness
7. 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 #9 Document tool used and score vs. baseline: _____	**No:** Go to #8
8. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness
9. Is the request for an increased cumulative dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #10	**No:** Go to #13
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12

12. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #13	**No:** Pass to RPh; deny; medical appropriateness
13. Does the patient have any of the following risk factors for overdose? a. Concomitant CNS depressants (benzodiazepines, muscle relaxants, sedating antipsychotics, etc) b. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 c. Recent urine drug screen indicating illicit or non-prescribed opioids d. Concurrent short- and long-acting opioid use	**Yes:** Go to #14 Document number of risk factors	**No:** Go to #15
14. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #15	**No:** Pass to RPh. Deny. Medical appropriateness
15. Does the patient have a pain contract on file with the prescriber?	**Yes:** Approved duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=3: 2 month 1-2: 4 months 0: 6 months	**No:** Pass to RPh. Deny; medical appropriateness

*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 following guidelines on opioid prescribing:

- 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 decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, 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, allowing for pauses during the taper, 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 an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:
    a. Assess for substance use disorder and transition to appropriate medication assisted treatment 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. May consider starting with a taper of ≤10% of the original dose per month 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 pharmacological and non-pharmacological 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. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
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: *2/20 (SS), 9/19 (DM), 3/17 (MH); 11/16; 05/16*
Implementation: *3/1/2020; 10/1/19*

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:

Initial: 7 to 30 days (except 12 months for end-of-life, sickle cell disease, severe burn injury, or cancer-related pain)
Renewal: Up to 6 months

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 14 days. Each prescription is limited to 7 days in treatment-naïve patients. Patients may fill up to 2 prescriptions every 90 days without prior authorization.
- All codeine and tramadol products for patients under 19 years of age

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.

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. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.

Approval Criteria

1. What is the patient's diagnosis?	Record ICD10	
2. Has the patient been prescribed any opioid analgesics (short or long-acting) for more than 6 weeks?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis funded by the OHP? Note: Currently, conditions such as fibromyalgia, TMJ, pelvic pain syndrome, neuropathy, and tension headache are not funded by the OHP.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
4. Is the requested medication a preferred agent?	**Yes:** Go to #6	**No:** Go to #5
5. 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 #6
6. 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 #7
7. 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 #8

8. 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 #9
9. 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 #10
10. 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 month and verified that opioid prescribing is appropriate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. 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:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12

12. Within the past 6 weeks, has a 5-day trial of at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried for this indication at its maximum effective dose and found to be ineffective or are contraindicated?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #14	**No:** Approve for up to 30 days
14. 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, weight loss, massage therapy, or acupuncture?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. 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 #16
16. 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, 3-item PEG scale, and MSPQ)?	**Yes:** Approve for up to 7 days not to exceed 90 MME	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**

3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #5 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness
5. 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 1 month that opioid prescribing is appropriate?	**Yes:** Go to #6	**No:** Pass to RPh. Deny. Medical appropriateness
6. 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 #7	**No:** Pass to RPh. Deny. Medical appropriateness
7. 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 #9 Document tool used and score vs. baseline: _____	**No:** Go to #8
8. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness

9. Is the request for an increased cumulative daily dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #10	**No:** Go to #12
10. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #12	**No:** Pass to RPh; deny; medical appropriateness
12. Does the patient have any of the following risk factors for overdose? a. Concomitant CNS depressants (benzodiazepines, muscle relaxants, sedating antipsychotics, etc) b. Total daily opioid dose > 90 MME or prescribed concurrent short- and long-acting opioids c. Recent urine drug screen indicating illicit or non-prescribed opioids	**Yes:** Go to #13 Document number of risk factors	**No:** Go to #14
13. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #14	**No:** Pass to RPh. Deny. Medical appropriateness

14. Does the patient have a pain contract on file with the prescriber?	**Yes:** Approved duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=3: 2 month 1-2: 4 months 0: 6 months	**No:** Pass to RPh. Deny; medical appropriateness

*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 following guidelines on opioid prescribing:

- 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 decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, 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, allowing for pauses during the taper, 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 an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:

a. Assess for substance use disorder and transition to appropriate medication assisted treatment 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. May consider starting with a taper of ≤10% of the original dose per month 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 pharmacological and non-pharmacological 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. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
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: *2/20 (SS), 9/19 (DM), 11/16 (AG)*
Implementation: *3/1/2020; 10/1/2019; 8/21/17*

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Policy Evaluation: Short-Acting Opioid Quantity Limits

Research Questions:

1. Since implementation of 7-day quantity limits for short-acting opioids, has the number of patients prescribed opioids for more than 7 days decreased?
2. Have there been changes in type of opioids prescribed (long- vs. short-acting) or average daily dose of prescribed opioids?
3. Has the number of patients with risk factors for overdose and long-term opioid use decreased since implementation of short-acting opioid quantity limits?
4. Has there been an increase in emergency department visits or hospitalizations for patients with denied opioid claims?
5. Has there been an increase in naloxone prescribing for patients claims for opioids?

Conclusions:

1. Proportion of patients with a 7 days' supply of opioids
    - The total number of patients with paid or denied claims for opioids decreased from 4916 patients in the 6 months before the policy implementation to 4279 in the 6 months after implementation of days' supply limits.
    - More patients had a denied claim (and no subsequent paid claims) for an opioid after implementation of these limits (18.2% vs. 7.4% before implementation).
    - A slightly larger proportion of patients had paid opioid claims for less than 7 days (67.5% of patients compared to 61.8% prior to implementation).
2. Type of opioids prescribed (long- vs. short-acting)
    - In patients with a claim for a short-acting opioid, over 98% of patients had claims for only short-acting opioids over a 90-day period. Few patients are prescribed combination use with a short-acting and long-acting opioid.
3. Daily dose
    - Overall, the average dose in morphine milligram equivalents (MME) per day was unchanged in the 6 months before and after the policy implementation.
    - About 60% of prescriptions were written for less than 30 MME per day and less than 2% of patients were prescribed greater than 90 MME per day.
4. Risk factors for overdose
    - In the overall population, the proportion of patients with use of concomitant sedating prescriptions for more than 14 days decreased in the 6 months after the policy implementation (from 7.6% to 2.8%).
    - There was a slight decrease in patients on high-dose opioids (>90 MME daily) from 20% to 18%, but other risk factors for overdose remained relatively unchanged. About 4% of patients prescribed opioids had a diagnosis of opioid use disorder (OUD), 22% had any type of substance use disorder, and 1% (n=42) had a recent overdose in the prior 90 days.

5. Emergency department (ED) visits and hospitalizations
    - In patients prescribed an opioid, the total number of all-cause ED visits was similar in the 6 months before and after implementation of days' supply limits. Approximately 44% of patients had an ED visit during this period and 19% were hospitalized. About half of all visits occurred following an opioid prescription. In the 6 months before the policy implementation, 2185 patients accounted for 4933 ED visits (average 2.25 visits per patient). A similar number of visits occurred in the 6 months following the policy implementation (4149 ED visits in 1903 patients; average 2.18 ED visits per patient).
    - Similar trends were observed for hospitalizations with the total number of hospitalizations remaining unchanged after the policy implementation.
6. Naloxone prescribing
    - The proportion of patients with claims for naloxone in the 90 days after the first opioid prescription remained small (about 1% of patients). However, this analysis did not evaluate prior history of naloxone prescriptions.

Recommendations:

- Modify criteria of current high-risk opioid retroDUR program to include patients who may be paying cash for chronic opioid prescriptions and patients with a diagnosis of substance abuse or history of overdose. Notify providers about risk mitigation strategies and opportunities to improve care (**Appendix 2**).

Background:

The Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was signed into law on October 24, 2018.[1] This law requires state Medicaid programs to have drug utilization review safety edits for opioid refills and an automated claims review process to identify refills in excess of state defined limits, monitor concurrent prescribing of opioids with benzodiazepines or antipsychotics, and require managed care plans to have these processes in place by October 1, 2019.[1] In accordance with these state defined limits, FFS criteria were updated to limit use of short-acting opioids to 7 days per prescription, 90 MME daily, and 2 prescriptions every 90 days. Quantities in excess of days' supply limits can be approved if prior authorization (PA) criteria are met. Current criteria require documentation of improvement in pain or function, evaluation of the Prescription Drug Monitoring Program (PDMP), urine drug screen, and assessment of risk factors for overdose including use of concurrent sedatives before long-term use of opioids can be approved.

In order to satisfy requirements for the SUPPORT Act, several other initiatives were implemented at the same time. Prior authorization was implemented for all long-acting opioid formulations. A retroDUR provider fax program targeted patients on concomitant sedatives and opioids. Faxes were sent to providers if their patient received an opioid and another sedative from different providers. A second retroDUR initiative involved profile review of patients who received opioids in excess of state defined quantity limits (e.g., more than 90 MME per day, more than one type of opioid, combination benzodiazepine use, multiple early refills, etc). For both retroDUR programs, providers were notified regarding potential risks with included suggestions for care coordination and mitigation strategies. In many cases, these initiatives overlap with short-acting opioid quantity limits, and patients may have been included in multiple programs. It is difficult to determine which program may have had the most impact on changes in opioid prescribing. In 2021, several additional changes were made to the SUPPORT Act which require the state to set minimum standards for monitoring in several new areas.[2] Areas of focus include monitoring for patients with a diagnosis of OUD prescribed subsequent opioids and assessment of patients at high risk for overdose.[2]

Methods:

This is a before-and-after analysis evaluating patients with a prescription for a short-acting opioid in the 6 months before and after implementation of the days' supply limits on 10/1/2019. The index event (IE) was classified as the first paid or denied FFS claim for a short-acting opioid in the reporting period (PDL class: opioids, short-acting). Denied claims were included based on error codes in **Table A1** and any denied claims with error codes associated with **Table A2** were excluded (see **Appendix 1**). If patients had both a paid and denied claim on the same date, the claim was classified as a paid IE. Patients were then categorized according to the duration of opioid use paid for by FFS in the 90 days following the IE. Patients with Medicare (benefit packages BMM, BMD, MED) or limited drug coverage (benefit packages CWM, MND, SMF, SMB) were excluded from the analysis. Patients with less than 75% Medicaid eligibility in the 6 months before or 3 months after the index event were excluded in order to ensure complete data was captured for included patients.

The following definitions and timeframes were used for this analysis:

- Duration of opioid therapy was defined using the cumulative days' supply from paid FFS opioid claims and was evaluated in the 3 months following the IE. The IE was included in days' supply calculations.
- Type of opioid was defined according to PDL class (short-term and long-term).
- Daily dose was defined based on average morphine milligram equivalents (MME) per day.
- New start patients were classified as patients with no opioid use (short or long-acting) in the 90 days before the IE. Patients with a prior history of opioid use were defined as patients with paid opioid claims (FFS or CCO) in this same timeframe.
- Prescriber type was identified using the primary provider specialty.
- Risk factors for overdose
    - Concurrent prescribing of sedating medications was evaluated in the 30 days before and after the IE. Because opioids are often prescribed for short durations, patients with concurrent sedative prescribing were defined based on duration of overlapping therapy: either 2 consecutive days in overlapping therapy, or more than 14 days of overlapping therapy with no more than a 4 day gap in concomitant use. Sedating medications included in the analysis were categorized by type of medication and included the following classes:
        - Muscle relaxants, oral
        - Sedatives
        - Benzodiazepines
        - Antipsychotics, 2nd gen
        - Select antiepileptics: gabapentin (HSN 008831), pregabalin (HSN 026470), phenobarbital (HSN 001561)
    - Cumulative average opioid dose greater than 90 MME per day
    - Claims for both a short and long-acting opioid in the 90 days following the IE
    - Diagnosis of opioid (ICD-10: F11x) or other substance abuse, dependence or use (ICD-10: F10x-F19x) was identified based on medical claims in the 2 years before the IE. Diagnosis history may be incomplete for patients who were recently enrolled in Medicaid.
    - Diagnosis on any medical claim indicating narcotic or sedative overdose in the 3 months before the IE (see **Appendix 1** for list of included ICD-10 codes)
- Prescriptions for naloxone (HSN 001874) were evaluated in the 7 days before or 90 days after the IE.
- Hospitalizations and ED visits occurring during the study period were identified for patients in the pre-specified populations. Since patients may have had multiple paid or denied claims, visits were categorized according to the most recent paid or denied opioid claim occurring within 90 days before the encounter and grouped into the following categories:

    1) visits with a paid opioid claim prior to the event

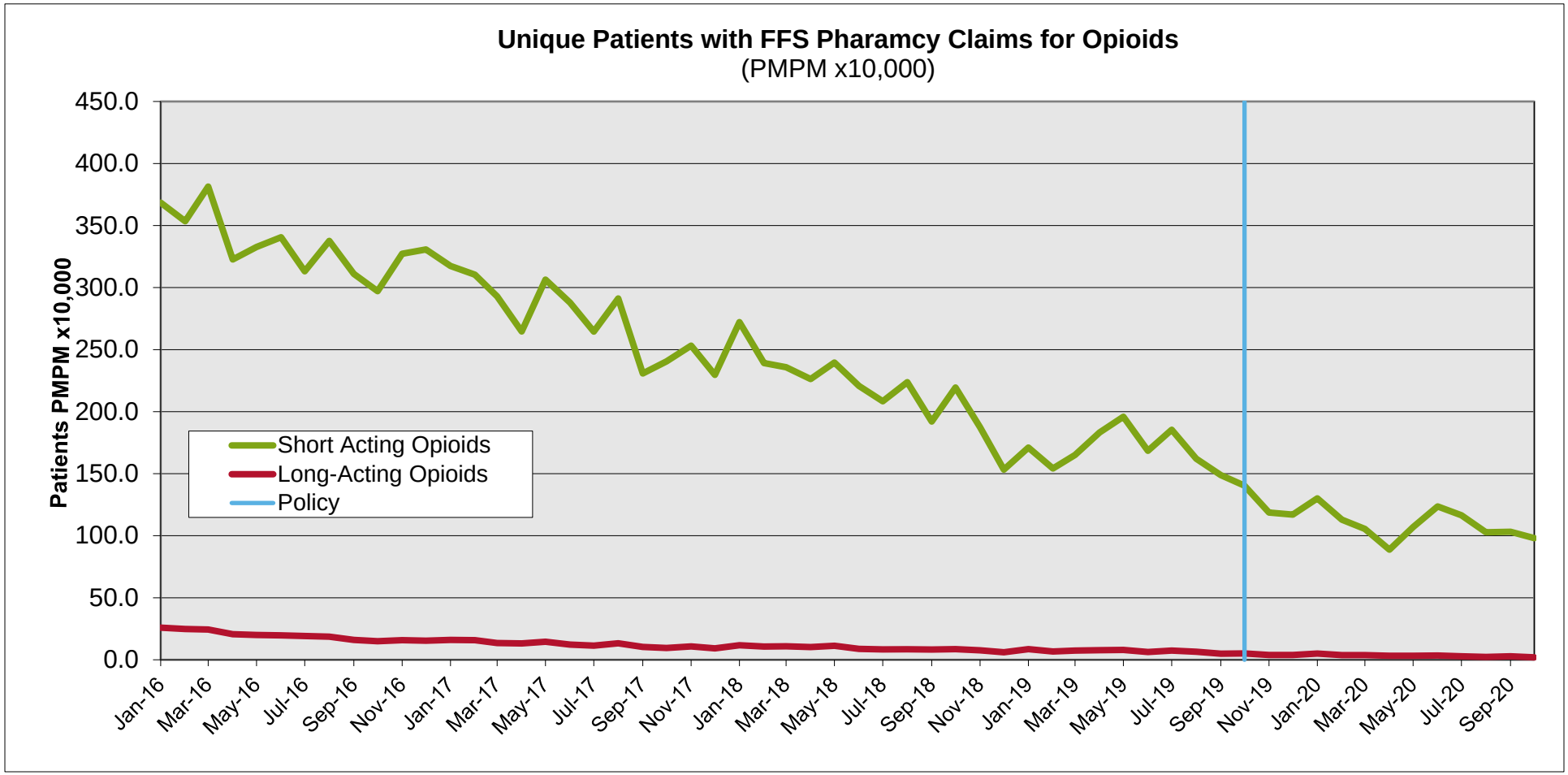
2) visits with a denied opioid claim prior to the event
3) visits without an opioid claim within 90 days before the event

If a patient had both a paid and denied claim on the same day, the encounter was categorized as paid. This analysis captures all ED visits or hospitalizations for the patients during the study period, and patients would be counted more than once if they had multiple medical visits. Subsequently, data for this analysis may be more heavily influenced by members with frequent ED visits or hospitalizations.

Results:

The number of medicaid patients prescribed opioids has decreased steadily in the past few years (**Figure 1**). The majority of patients have prescriptions for short-acting opioids and relatively few patients are prescribed long-acting opioids.

Figure 1. Per member per month (PMPM) count of patients with a prescription for an opioid from 2016 to present. Policy implementation date was 10/1/2019. Type of opioid was categorized according to PDL class.



Basic patient characteristics at the time of the first opioid claim are shown in **Table 1**. The total number of patients with paid or denied claims for opioids decreased from 4916 patients in the 6 months before the policy implementation to 4279 in the 6 months after implementation of days' supply limits. The majority of prescriptions were for adults (92%) and females (69%). Approximately 32% of patients were white and 34% identified as American Indian or Alaskan Native. Only 2% of patients had a hospital discharge within 7 days prior to the first opioid prescription. Populations were similar in the 6 months before and after the IE.

Table 1: Demographics at the time of the IE.

	Before	After
N=	4916	4,279

Age				
<=18	433	9%	338	8%
19-64	4473	91%	3,930	92%
>=65	10	0%	11	0%
Race				
White	1506	31%	1,353	32%
American Indian/Alaskan Native	1628	33%	1,472	34%
Other	387	8%	333	8%
Unknown	1395	28%	1,121	26%
Female	3378	69%	2,951	69%
Inpatient hospital discharge date within 7 days before IE	117	2%	97	2%

After implementation of days' supply edits, patients were allowed to fill 2 prescriptions of up to 7 days without a PA. PA was required for more than 2 prescriptions within a 90 day timeframe or for any single prescription greater than 7 days. After implementation of these limits, there was an increased number of patients with denied claims (shown as patients with 0 days' supply in **Table 2**), and a slight increase in the proportion of patients prescribed opioids for less than 7 days (67.5% compared to 61.8% prior to implementation). Similarly, there was a decreased number of patients with paid opioid prescriptions for more than 14 in the 6 months after the policy implementation (7.7%) compared to the control period (21.5%). Similar trends were observed in patients newly started on opioids and in those with a history of opioid prescribing in the prior 90 days (**Table 2**). Of all patients prescribed opioids in the 6 months following implementation, 77% were patients with no recent opioid use. Of these, 41% of patients with an initial denied prescription and no subsequent paid claims (n=319 of 780 total) were patients with no opioid use in the previous 90 days.

Table 2. Days' Supply in the 90 days following the first opioid claim

	Before		**After**	
N=	**4,916**		**4,279**	
All Patients				
0 days	366	7.4%	780	18.2%
1-7 days	3,039	61.8%	2,888	67.5%
8-14 days	456	9.3%	280	6.5%
>14 days	1,055	21.5%	331	7.7%
N=	**3709**	**%**	**3291**	**%**

New Start				
0 days	86	2.3%	319	9.7%
1-7 days	2,782	75.0%	2,661	80.9%
8-14 days	348	9.4%	240	7.3%
>14 days	493	13.3%	71	2.2%
N=	**1207**	**%**	**988**	**%**
Prior Opioid History				
0 days	280	23.2%	461	46.7%
1-7 days	257	21.3%	227	23.0%
8-14 days	108	8.9%	40	4.0%
>14 days	562	46.6%	260	26.3%

Because multiple point-of-sale edits were implemented at the same time period, there may be multiple reasons for paid or denied claims. For example, patients may have an initial denied claim if it was billed for greater than 7 days, but receive a subsequent paid claim pharmacy decided to dispense a partial prescription or the provider decreased the prescription quantity. Other patients may have an initial paid claim for less than 7 days, but a have a subsequent denial for another prescription if they continue to be prescribed opioids for longer than 14 days. **Table 3** shows patterns of paid and denied claims for the IE and in the subsequent 90 days. In the 6 months after the implementation of 7 day supply limits, the proportion of patients with an initial paid claim decreased from 90% to 77%. More than half of patients (62%) had only paid claims for opioids indicating they were prescribed within the recommended days' supply limits. Twenty percent of patients had both paid and denied claims, indicating they were impacted by the policy, but had received a paid opioid prescription. Eighteen percent of patients had only denied claims for opioids indicating that while they were prescribed an opioid, it was never paid for by FFS Medicaid. As expected, the proportion of patients with at least one denied claim increased after implementation of the days' supply limits from 7% to 18% for patients without any paid opioid claims and from 12% to 20% in patients with at least one denied claim. The total number of patients with more than one claim for an opioid has decreased over time indicating that prescribers continue to write fewer prescriptions for short-acting opioids (from 1658 patients in the 6 months before to 1518 patients in the 6 months after the policy implementation). In patients with more than one claim, they were more likely to have subsequent denied opioid prescription in the 6 months after implementation of the policy (48% of patients with more than one claim) compared to 22% in the control period.

Table 3. Claim types and prescription characteristics

	Before		After	
N=	**4,916**		**4,279**	
Initial IE (first claim)				
Paid	4,414	90%	3,303	77%
Denied	502	10%	976	23%
FFS Claim types in 90 days after IE				

Paid only	3,938	80%	2,658	62%
Denied only	366	7%	780	18%
Paid and denied	612	12%	841	20%
Last FFS opioid claim in the 90 days after the IE (for patients with >1 claim) N=	**1,659**		**1,518**	
Paid	1,295	78%	781	51%
Denied	364	22%	737	49%

Table 4 shows the days' supply of opioids paid for by FFS Medicaid within 90 days of an initial claim. In patients with an initial paid claim the proportion of patients with less than 7 days of opioids increased from 68% to 84%. In patients with an initial denied claim, the majority of patients (79%) had no subsequent paid claim. Only a small proportion of patients with an initial denial had subsequent paid claims for less than 7 days (10%), 7 to 14 days (3%) or greater than 14 days (7%).

Table 4. Days' Supply based on the disposition of the initial IE

	Before		After	
Paid IE N=	**4,414**	**%**	**3,303**	**%**
1-7 days	3,021	68.4%	2,791	84.5%
8-14 days	450	10.2%	251	7.6%
>14 days	943	21.4%	261	7.9%
Denied IE N=	**502**	**%**	**976**	**%**
0 days	366	72.9%	780	79.9%
1-7 days	18	3.6%	97	9.9%
8-14 days	6	1.2%	29	3.0%
>14 days	112	22.3%	70	7.2%

In patients with a claim for a short-acting opioid, over 98% of patients had claims for only short-acting opioids over a 90-day period (**Table 5**). A small proportion of patients were prescribed long-acting opioids or long-acting opioids in combination with a short-acting product. The number of patients prescribed multiple opioid products has decreased since implementation of the policy.

Table 5. Type of opioid prescribed for the IE and in the 90 days after the IE

	Before		After	
N=	**4,916**	**%**	**4,279**	**%**

Short-acting opioid (paid claims)	4,478	91%	3,457	80.8%
Short-acting opioid (single denied claim)	366	7%	780	18.2%
Long-acting opioid only	11	0%	20	0.5%
Rx for both short-and long-acting opioids	61	1%	22	0.5%

Overall, the average dose in morphine milligram equivalents (MME) per day was unchanged in the 6 months before and after the policy implementation (**Table 6**). About 60% of prescriptions were written for less than 30 MME per day and less than 2% of patients were prescribed greater than 90 MME per day. When evaluating dose based on the days' supply, the largest changes after the policy occurred in patients on lower doses. More patients with less than 30 MME per day had denied prescriptions (3.7% before vs. 11.9% after policy implementation) and fewer patients had more than 14 days of opioid therapy paid by Medicaid (14.1% before vs. 4.5% after policy implementation). About 33% of patients before the policy and 34% of patients after the policy had claims with more than one prescription number indicating that these patients had a subsequent opioid prescription written in the following 90 days. Similar trends in daily dose were observed for patients with more than one claim in the 90 days following the IE.

Table 6. Average Daily Dose

	Before		After	
N=	**4,916**	**%**	**4,279**	**%**
Average Daily Dose IE				
<= 30 MME/day	2,906	59.1%	2,589	60.5%
31-60 MME/day	1,514	30.8%	1,264	29.5%
61-90 MME/day	405	8.2%	354	8.3%
>= 91 MME/day	91	1.9%	72	1.7%

Patients with several risk factors for overdose were evaluated in patients with paid or denied claims for opioids (**Table 7**). In the overall population, the proportion of patients with use of concomitant sedating prescriptions for more than 14 days decreased in the 6 months after the policy implementation (from 7.6% to 2.8%). It is unclear if this change is due to discontinuation of the opioid or sedative. The majority of patients with concomitant sedating prescriptions occurred in patients prescribed opioids for more than 14 days. Of the 331 patients prescribed more than 14 days of opioids in the 6 months after the policy implementation, approximately 36% (n=119) were prescribed a concomitant sedating medication which is similar to the 6 months prior to policy implementation (376 of 1055 patients, 36%). There was a slight decrease in patients on high-dose opioids (>90 MME daily) from 20% to 18%, but other risk factors for overdose remained relatively unchanged. **Table 8** examines risk factors in more detail according to days' supply for paid prescriptions in the 90 days following the first opioid claim.

Table 7. Patients with risk factors for overdose in the 90 days following the IE

	Before		After	
N=	**4916**	**%**	**4279**	**%**

Concomitant sedative				
>= 2 consecutive days	268	5.5%	131	3.1%
>= 14 days	376	7.6%	121	2.8%
Short and long acting opioid claims	81	1.6%	72	1.7%
Patients with average cumulative daily dose >90 MME for opioid covered days	1006	20.5%	782	18.3%
Diagnosis for opioid use disorder in 90 days prior to IE (F11x)	192	3.9%	167	3.9%
Diagnosis for substance use disorder in 90 days prior to IE (F10x-F19x)	1154	23.5%	961	22.5%
Recent overdose in 90 days prior to IE	42	0.9%	42	1.0%
Number of risk factors (mutually exclusive)				
1	1640	33.4%	1384	32.3%
2	420	8.5%	305	7.1%
3	60	1.2%	39	0.9%
4	7	0.1%	1	0.0%
5	2	0.0%	1	0.0%
Naloxone prescription in 7 days before or after IE	44	0.9%	57	1.3%

After implementation of the days' supply policy, there was a slightly greater number of patients with denied claims only for both short-acting and long-acting opioids (n=20, 0.5% of the total population) compared to the period before the policy implementation (n=2, 0%). Similarly, fewer patients with diagnoses of OUD or any substance use disorder received opioids from Medicaid for longer than 14 days after implementation of days' supply edits (**Table 8**). Opioid use disorder was defined according to ICD-10 codes and included codes for opioid dependence, opioid abuse, and opioid use. In patients with a diagnosis of OUD, patients with prescriptions for more than 14 days decreased from 1.2% (n=61) to 0.4% (n=17) and the proportion of patients who had no paid prescriptions for an opioid despite having a prescription increased from 0.5% (n=24) to 1.0% (n=42). Similar trends were noted in all patients with a diagnosis of any substance use disorder with a greater number of patients with no paid claims for their opioid prescription after implementation of the policy. In patients with an overdose in the past 90 days, there were more patients with 0 to 7 days' supply compared to patients in the 6 months before the policy implementation. While the number of patients with a recent overdose is relatively small (42 patients over 6 months), It is concerning that patients with a recent overdose continue to have prescriptions written for opioids.

Table 8. Risk factors for overdose based on days' supply

		Before		**After**	
	N=	**4916**	**%**	**4279**	**%**
Short and long acting opioid claims		81	1.6%	72	1.7%
0 days		2	0.0%	20	0.5%

1-7 days	2	0.0%	6	0.1%
7-14 days	2	0.0%	3	0.1%
>14 days	75	1.5%	43	1.0%
Patients with average cumulative daily dose >90 MME for opioid covered days	1006	20.5%	782	18.3%
0 days	0	0.0%	0	0.0%
1-7 days	955	19.4%	767	17.9%
7-14 days	11	0.2%	1	0.0%
>14 days	40	0.8%	14	0.3%
Diagnosis for opioid use disorder in 90 days prior to IE (ICD-10: F11x)	192	3.9%	167	3.9%
0 days	24	0.5%	42	1.0%
1-7 days	92	1.9%	96	2.2%
7-14 days	15	0.3%	12	0.3%
>14 days	61	1.2%	17	0.4%
Diagnosis for substance use disorder in 90 days prior to IE (ICD-10: F10x-F19x)	1154	23.5%	961	22.5%
0 days	84	1.7%	168	3.9%
1-7 days	677	13.8%	648	15.1%
7-14 days	114	2.3%	78	1.8%
>14 days	279	5.7%	67	1.6%
Recent overdose in 90 days prior to IE	42	0.9%	42	1.0%
0 days	5	0.1%	12	0.3%
1-7 days	15	0.3%	23	0.5%
7-14 days	8	0.2%	2	0.0%
>14 days	14	0.3%	5	0.1%
Naloxone prescription in 7 days before or after IE	44	0.9%	57	1.3%
0 days	4	0.1%	13	0.3%
1-7 days	13	0.3%	29	0.7%
7-14 days	3	0.1%	5	0.1%
>14 days	24	0.5%	10	0.2%

Provider specialty for the initial opioid claim is shown in **Table 9**. For the majority of patients, the first prescription in the reporting period was prescribed from a family provider (15%), physician assistant (12%), emergency room provider (10%), obstetrics and gynecology specialist (10%), or family nurse practitioner (9%). Overall, the proportion of patients receiving opioid claims from each specialty was similar in the 6 months before and after the implementation of days' supply

limits. For almost all specialties, there were a greater number of patients who had no opioids paid by FFS and fewer patients with paid opioid prescriptions of more than 14 days after the policy implementation.

Table 9. Top 20 prescriber specialties associated with the IE

		Before		After	
	N=	4,916	%	4,279	%
1	Family Practitioner	682	13.9%	652	15.2%
2	Physician Assistants	642	13.1%	508	11.9%
3	Emergency Med Practitioner	486	9.9%	442	10.3%
4	Obstetrics & Gynecology	468	9.5%	426	10.0%
5	Family Nurse Practitioner	395	8.0%	367	8.6%
6	Gen. Dentistry Practitioner	369	7.5%	289	6.8%
7	Internist	298	6.1%	266	6.2%
8	Dentist (Default Spec)	175	3.6%	190	4.4%
9	Oral Surgeon	192	3.9%	134	3.1%
10	Orthopedic Surgeon	165	3.4%	154	3.6%
11	General Surgeon	127	2.6%	123	2.9%
12	Nurse Practitioner (default Spec)	118	2.4%	102	2.4%
13	Advance Practice Nurse	104	2.1%	62	1.4%
14	Physician (Default Spec)	57	1.2%	62	1.4%
15	Certified Nurse Midwife	60	1.2%	46	1.1%
16	Otologist, Laryngologist, Rhinologist	63	1.3%	37	0.9%
17	Physical Medicine and Rehabilitation Practitioner	39	0.8%	39	0.9%
18	Urologist	37	0.8%	32	0.7%
19	UNKNOWN	54	1.1%	8	0.2%
20	Pediatrics	32	0.7%	28	0.7%

In total, 1621 patients had at least one denied claim in the 6 months after implementation of days' supply limitations compared to 978 patients in the 6 months prior to implementation. Approximately 32% of these patients had a subsequent paid claim within 30 days and another 6% of patients had a paid claim within 90 days. However, most patients who received a denial had no paid claims (62%) or prior authorization requested (60%) in the 90 days after their denial (increased from 50% and 47% in the period before the policy implementation, respectively). Upon evaluation of prior opioid history, 42% of patients with a denied claim were new start patients.

Table 10. Outcomes for patients with any denied claim in the 90 days after the IE. In order to avoid counting patients multiple times, the first denial for each patient was used. Outcomes were evaluated in the 90 days following the initial denial.

	Before		After	
N=	978	%	1,621	%

Denied Claim				
Opioid paid within 30 days after the denial	380	38.9%	519	32.0%
Opioid paid within 31-90 days after denial	112	11.5%	95	5.9%
Never had an opioid paid within 90 days of denial	486	49.7%	1,007	62.1%
PA not requested within 5 days before or 90 days after the denial	462	47.2%	976	60.2%
PA denied within 5 days before or 90 days after the denial	26	2.7%	58	3.6%
Never received opioid and had diagnosis of malignant neoplasm (ICD-10 Cx) or end of life diagnosis (Z515)	28	2.9%	46	2.8%
Prior opioid history in patients with a denied claim				
Opioid paid within 30 days before the denial	476	48.7%	740	45.7%
Opioid paid within 31-90 days before the denial	103	10.5%	195	12.0%
Never had an opioid paid within 90 days before the denial	399	40.8%	686	42.3%

Table 11 shows the number of emergency department visits and hospitalizations during the study period for identified patients with a paid or denied opioid claim. Overall, the total number of ED visits and hospitalizations was unchanged in the 6 months before and after the policy implementation. In the 6 months before the policy implementation, there were a total of 4933 ED visits in 2185 patients (on average 2.25 visits per patient for those with a ED visit). A similar number of visits occurred in the 6 months following the policy implementation (4149 visits in 1903 patients; average 2.18 ED visits per patient). Almost half of these visits appear to be unrelated to opioid use. The number of visits occurring in the 90 days following a denied claim increased from 5% to 15% of visits and there was a decrease in visits occurring following a paid opioid claim. Similar trends were observed for hospitalizations. This is not unexpected as the number of patients with denied opioid claims increased after implementation of the policy. Because of multiple confounding factors, it is difficult to draw firm conclusions about whether ED visits are correlated to denied opioid prescriptions. One limitation of this analysis is that patients could be included in both the before and after groups. Patients were included in both groups in order to capture data on patients with a history of chronic opioid use. While increases in ED visits were observed in patients with denied opioid claims, a proportional decrease was observed in patients with paid opioid claims. It is possible that the same patients were included in both the before and after group and have just been categorized differently based on a denied claim in the 6 months after the policy implementation.

Upon evaluation of primary diagnoses associated with ED visits, the most common diagnoses associated with ED visits were comparable in the 6 months before and after the implementation of days' supply limits. Common diagnoses for ED visits included abdominal and pelvic pain, pain in throat and chest, dorsalgia, other pain, and other joint disorder. These diagnoses, occurring both before and after the policy implementation, indicate that pain continues to be a complex condition to adequately control. In patients with an ED visit or hospitalization following a paid or denied opioid claim, visits associated with diagnoses of OUD, overdose, or any substance use disorder were infrequent (<0.3% of patients prescribed opioids) and few patients had medical claims indicating naloxone administration in a hospital or outpatient setting. However, this data is unlikely to capture naloxone administration which occurs outside the hospital setting and is administered by non-medical personnel (e.g., patient, family, friends, etc.) or by emergency medical services.

Table 11. ED visits and hospitalizations for patients with claims for opioids.

	Before		After	
N=		%		%
All-cause ED visits	4,933		4,149	
Paid FFS opioid claim (short or long acting) within 90 days prior to the visit	2,345	47.5%	1,472	35.5%
Denied FFS opioid claim (short or long acting) within 90 days prior to the visit	252	5.1%	616	14.8%
No FFS opioid claim (paid or denied) within 90 days prior to the visit	2,336	47.4%	2,061	49.7%
All-cause hospitalizations (unique admissions)	1,186		1,017	
Paid FFS opioid claim (short or long acting) within 90 days prior to the hospitalization admission	278	23.4%	175	17.2%
Denied FFS opioid claim (short or long acting) within 90 days prior to the hospitalization admission	45	3.8%	73	7.2%
No FFS opioid claim (paid or denied) within 90 days prior to the hospitalization admission	863	72.8%	769	75.6%

Limitations:

Data presented in this report is based on Medicaid claims history and has several inherent limitations.

- Diagnostic accuracy: Diagnoses based on claims history may be inaccurate or incomplete. Because diagnoses are not associated with prescriptions, it is difficult to determine the intended indication for the drug, particularly when therapy is used off-label.
- Provider specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified.
- Days' Supply Estimates: Estimates of days' supply attempts to estimate the duration a patient has been prescribed opioids, but may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately. Days' Supply only captures claims paid by FFS and excludes any claims paid for by CCOs, by other insurances, or by the patient.
- Definitions for new start patients: Prior use of opioids was only evaluated in the 90 days prior to the IE. If patients have been paying cash for their opioid prescription, they may be inaccurately categorized as a new start patient because of the lack of paid claims.
- Utilization, particularly medical and hospital visits may be partially impacted by the COVID pandemic in the time after the policy (10/1/19 to 3/31/20). Medical visits were evaluated in the 90 days following a paid or denied opioid claim and for some patients, this period could have occurred when general medical offices were closed and stay-at-home orders were in place.
- The retrospective nature of the study also does not control for potential unknown confounders which may influence results of the analysis. Multiple prospective and retrospective initiatives were implemented during the same period and it is difficult to discern which initiatives had the greatest impact. Other potential confounders include changes in the population over time or changes in the general prescribing patterns of providers. For example, national and state programs to monitor overdose rates and increase access to counseling and medication assisted treatment for OUD may influence patterns of opioid prescribing. Similarly, ED visits and hospitalizations may be influenced by a variety of factors. Patients with more severe illness or breakthrough pain are more likely to have denied claims due to changes in therapy and are also likely to visit the ED more frequently.

References:

1. The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act. https://www.congress.gov/bill/115th-congress/house-bill/6. Accessed March 20, 2019.
2. Medicaid Program; Establishing Minimum Standards in Medicaid State Drug Utilization Review (DUR) and Supporting Value-Based Purchasing (VBP) for Drugs Covered in Medicaid, Revising Medicaid Drug Rebate and Third Party Liability (TPL) Requirements. A Rule by the Health and Human Services Department, and the Centers for Medicare & Medicaid Services. Federal Register: The Daily Journal of the United States Government. https://www.federalregister.gov/documents/2020/12/31/2020-28567/medicaid-program-establishing-minimum-standards-in-medicaid-state-drug-utilization-review-dur-and. Updated December 31, 2020. Accessed February 26, 2021.

Appendix 1: Drug Coding

Table A1. Included error codes for denied claims

Error Code	Error Status Description
6899	SHORT-ACTING OPIOID MAX 7-DAY SUPPLY EXCEEDED
6510	Pharmacy Opioid Limit - 2 Fills in 90 days
4165	DRUG QUANTITY PER DAY LIMIT EXCEEDED
4175	OPIATES DRUG QUANTITY PER DAY LIMIT EXCEEDED
3022	Non-Pref Drug. Prior Authorization Required.
3002	NDC REQUIRES PA
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE
4025	AGE IS NOT ALLOWED FOR NDC
4026	DAY SUPPLY LIMIT EXCEEDED FOR COVERED NDC

Table A2. Excluded error codes for denied claims

Error Code	Error Status Description
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
4999	THIS DRUG IS COVERED BY MEDICARE PART D
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
576	CLAIM HAS THIRD-PARTY PAYMENT
513	RECIPIENT NAME AND NUMBER DISAGREE
238	RECIPIENT NAME IS MISSING
2809	DOB IS INVALID
503	DATE DISPENSED AFTER BILLING DATE
5001	EXACT DUPLICATE

628	Other Coverage Reject Code Required for OCC 3
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER
500	DATE PRESCRIBED AFTER BILLING DATE
221	DAYS SUPPLY MISSING
502	DATE DISPENSED EARLIER THAN DATE PRESCRIBED
643	INVALID OTHER COVERAGE CODE
205	PRESCRIBING PROVIDER ID MISSING

Table A3. ICD-10 codes associated with poisoning by or adverse effect of various agents. Codes for underdosing are excluded.

ICD-10 codes	***Agent***
T400X1x- T400X5x	opium
T401X1x- T401X4x	heroin
T402X1x- T402X5x	other opioids
T403X1x- T403X5x	methadone
T40411x- T40415x	fentanyl or fentanyl analogs
T40421x- T40425x	tramadol
T40491x- T40495x	other synthetic narcotics
T405X1x- T405X5x	cocaine
T40601x- T40605x	other and unspecified narcotics
T40691x- T40695x	other narcotics
T407X1x- T407X5x	cannabis (derivatives)
T408X1x- T408X4x	lysergide [LSD]
T40901x- T40905x	other and unspecified psychodysleptics [hallucinogens]
T40991x- T40995x	other psychodysleptics [hallucinogens]
T420X1x- T420X5x	hydantoin derivatives
T421X1x- T421X5x	iminostilbenes
T422X1x- T422X5x	succinimides and oxazolidinediones
T423X1x- T423X5x	barbiturates
T424X1x- T424X5x	benzodiazepines
T425X1x- T425X5x	mixed antiepileptics
T426X1x- T426X5x	other antiepileptic and sedative-hypnotic drugs
T427X1x- T427X5x	unspecified antiepileptic and sedative-hypnotic drugs
T428X1x- T428X5x	antiparkinsonism drugs and other central muscle-tone depressants
T43011x-T43015x	tricyclic antidepressants
T43021x-T43025x	tetracyclic antidepressants

T431X1x-T431X5x	monoamine-oxidase-inhibitor antidepressants
T43201x-T43205x	other and unspecified antidepressants
T43211x-T43215x	serotonin and norepinephrine reuptake inhibitors
T43221x-T43225x	selective serotonin reuptake inhibitors
T43291x-T43295x	other antidepressants
T433X1x-T433X5x	phenothiazine antipsychotics and neuroleptics
T434X1x-T434X5x	butyrophenone and thiothixene neuroleptics
T43501x-T43505x	other and unspecified antipsychotics and neuroleptics
T43591x-T43595x	other antipsychotics and neuroleptics
T43601x-T43605x	psychostimulants
T43621x-T43625x	amphetamines
T43631x-T43635x	methylphenidate
T43641x-T43644x	ecstasy
T43691x- T43695x	other psychostimulants
T438X1x- T438X5x	other psychotropic drugs
T4391xx- T4395xx	unspecified psychotropic drug
T450X1x-T450X5x	antiallergic and antiemetic drugs
T481X1x-T481X5x	skeletal muscle relaxants [neuromuscular blocking agents]
T48201x-T48205x	other and unspecified drugs acting on muscles
T483X1x-T483X5x	antitussives
T485X1x-T485X5x	other anti-common-cold drugs
T50901x-T50905x	unspecified drugs, medicaments and biological substances
T50911x-T50915x	multiple unspecified drugs, medicaments and biological substances
T50991x-T50995x	medicaments and biological substances

Table A3. Health Outcome Codes

ED Visits	**Procedure Codes OR Revenue Center Codes**	**99281-99285, 99288 0450-0459 or 0981**
Hospitalizations	**Claim Type = I**	
Medical claims for naloxone administration	**CPT Code**	**J2310**

Appendix 2. RetroDUR Program for High-Risk Opioid Patients

- Inclusion criteria
  - Patients currently enrolled in FFS; AND
  - Patients with a paid or denied claim ~~current PA~~ for an opioid prescription within the past quarter; ~~(in at least one of the PDL classes: opioids, short-acting or opioids, long-acting) – Current PA defined as a PA with a start date before today and PA end date after today~~ AND
  - At least one of the following:
    1. High dose: Patients with cumulative opioid dose >90 MME (for all opioid formulations) for >60 days (with <=7 day gap in therapy) in a 120 day lookback; OR
    2. SAO and LAO: Patients with paid claims in the Opioids, Short-acting PDL class AND claims in the Opioids, Long-acting PDL class for >60 days overlap with <=7 day gap in therapy in a 120 day lookback; OR
    3. Multiple opioids: Patients with paid claims for 2 or more GSNs in a given opioid PDL class (opioids, short-acting or long-acting) for >60 days overlap with <=7 day gap in therapy in a 120 day lookback; OR
    4. >110% covered days: Patients with sum of >110% of covered days for a specific opioid (based on HSN) in a 120 day lookback (filling an extra 12 days of opioids approximately); OR
    5. Opioid and Benzodiazepine: Patients with paid claims for opioids (opioids, short-acting OR opioids, long-acting PDL classes) AND paid claims in the Benzodiazepines PDL class for >60 days overlap with <=7 day gap in therapy in a 120 day lookback; OR
    6. Multiple denied claims: Patients with >=3 unique denied claims for an opioid in the past 120 days which may indicate cash-paying (PDL classes: opioids, short-acting or opioids, long-acting). Count only denied claims for unique prescription numbers for which there is not a paid pharmacy claim for the same prescription number. Count each prescription only once if there are multiple denials for the same prescription number; OR~~.~~
    7. Overdose history: Patients with a history of opioid overdose in the past 2 years; OR
    ~~6.~~8. Substance use disorder: Patients with a diagnosis of substance use disorder (excluding alcohol) in the past 2 years or patients prescribed medication assisted treatment (PDL class: substance use disorders, opioid and alcohol) within the past 6 months.
- Exclusion criteria
  - Patients with a malignant cancer diagnosis (ICD-10 codes beginning with C) or claim for palliative care (Z51.5) based on medical claims in the past year
  - Patients with a diagnosis of sickle cell disease in the past year (ICD-10 D57xxx)
  - Patients with currently active primary insurance or Medicare coverage (this population will bypass our edits)
  - Patients previously reviewed with this initiative in the last 6 months
  - Patients who have had a provider letter sent regarding concomitant use of opioid and sedating medications in the past 6 months
- Prioritize patients based on the number of inclusion criteria are met (#1-8 above). Higher priority patients will meet more inclusion criteria.

Oregon Health Authority

Oregon State University College of Pharmacy

Prescriber alert:
High-risk Patient
On Opioid Therapy

Date: MM/DD/YYYY
To: Provider name
Address: Mailing address **City:** City
State: State **ZIP:** ZIP **Phone number:** ###-###-####
Fax number: ###-###-#### **Total pages:** #
Regarding patient: Name, Medicaid ID, DOB

Dear Physician/Allied Health Prescriber:

The Oregon Health Authority (OHA) reviews fee-for-service prescription medications dispensed and prescribed to Oregon Health Plan (OHP) members. Based on OHA's review of your patient's current opioid prescriptions, there is a high risk for adverse outcomes, as described below:

<Concern 1>

<Free-form Text (Rationale)>

<Concern 2>

<Free-form Text (Rationale)>

What should you do?

OHA offers the following recommendations to help ensure your patient's medication regimen is safe and appropriate:

- <Recommendation 1>
- <Recommendation 2>

Please consider these clinical recommendations then coordinate with co-prescribers and your patient as clinically appropriate. Thank you for continuing to serve OHP patients.

For resources regarding safe opioid prescribing see: *http://www.cdc.gov/drugoverdose/prescribingresources.html*

Concern: (drop-down choices)

(A) Patient with > 90 Morphine Milligram Equivalents (MMEs) cumulative daily dose

(B) Concurrent paid claims identified for short- and long-acting opioids

(C) Concurrent paid claims identified for ≥ 2 unique opioids

(D) Multiple paid claims identified for early opioid fills

(E) ≥ 3 unique denied claims identified for opioid prescriptions

(F) Paid claims identified for opioids and concurrent benzodiazepines or other sedative-hypnotic medications

(G) No evidence of naloxone prescription on profile

(H) History of overdose in the past year

(I) Diagnosis or prescriptions indicating a substance use disorder

Rationale: (RPh will enter free-form text in box)

[1] Above 90 mg MME, the risk of overdose death increases 10 times.

[2] CDC recommends that clinicians discuss with patients known risks and realistic benefits of opioid therapy and mutual responsibilities for managing therapy.

[3] Naloxone is a pure opioid antagonist that reverses opioid overdose when administered properly. CDC recommends co-prescribing naloxone to patients at elevated risk of overdose who receive opioid analgesia.

[4] CDC recommends that clinicians offer or arrange evidence-based treatment (usually medication assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

[5] When prescribing opioids for chronic pain, CDC recommends that clinicians use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

[6] If benefits do not outweigh harms of continued opioid therapy, CDC recommends clinicians optimize alternate therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids. CDC guidance for opioid dose reduction may be found at: https://www.hhs.gov/opioids/treatment/clinicians-guide-opioid-dosage-reduction/index.html

[7] Denied claims may indicate the pharmacy is trying to fill the prescription early or your patient may be paying cash. Their current prior authorization (PA) for <drug name> expires on <XX/XX/XXXX>. The following information should be included with PA requests:

- A risk/benefit assessment including risk factors for overdose
- Objective documentation of improvement
- Documentation of a recent PDMP evaluation
- Documentation of a pain contract with the patient

[8] 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. Roughly 30% of opioid overdoses involve benzodiazepines.

[9] Opioids are associated with increased risk of dependence, abuse, and misuse. This risk may be increased in patients with a diagnosis of opioid or substance use disorder or in patients with a history of overdose.

Recommendation: (drop-down choices – *option for multiple selections)*

☐ Use extreme precaution when increasing opioid dose to ≥ 50 MME per day based on increased risk of overdose.

☐ Avoid daily opioid doses > 90 MME unless clinically justified.

☐ Evaluate benefits and harms of chronic opioid therapy every 3 months or more frequently.

☐ Optimize of multi-modal therapies to strategize with your patient to lower their daily opioid dose or to progress toward taper and discontinuation of opioids.

☐ Do not prescribe long-acting opioids for acute pain.

☐ Check the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) at least every 3 months to verify appropriate opioid prescribing.

☐ Mobilize care coordination services to assess if prescriptions are being used according to physicians' directions.

☐ Co-prescribe naloxone to patients at elevated risk of overdose.

☐ Discuss the risk/benefit of opioids with your patient and submit prior authorization for the prescribed opioid if appropriate.

☐ Use extreme caution when prescribing opioids to patients on chronic benzodiazepine or sedative-hypnotic medications.

☐ Use extreme caution when prescribing opioids to patients with opioid use disorder or recent overdose. Consider close monitoring as appropriate. Medication assisted therapy for opioid use disorder is available without prior authorization.

Minimum standards for DUR programs

The Oregon Health Authority (OHA) and contracted managed care entities (MCEs) must follow these standards on and after July 1, 2021, for most Oregon Health Plan members. These standards are pursuant to 42 CFR § 456.703(h) and the SUPPORT Act.

Exempt populations: Individuals receiving hospice, palliative care, or cancer treatment; residents of long-term care facilities described in 42 USC 1396a(oo)(3)(A)(ii); and individuals with sickle cell disease are exempt from these requirements. MCEs must ensure individuals in these categories continue to have appropriate access to opioid treatment.

1. Prospective "safety edit"[1] limitations and "claims review automated process"[2] for opioid fills above state-defined limitations for day supply and early refill

7-day supply limits for at least new starts of short acting opioids, and early refill thresholds to identify potential misuse or abuse.

- Thresholds must be equal to or more restrictive than general refill thresholds.
- Supply limits and early refill thresholds must be enforced by prior authorization (PA), quantity limits, or "soft edits" at point-of-sale.

Periodic claims review to look for concerning treatment (could include multiple prescribers, long courses of treatment, patients prescribed duplicate therapy, multiple early refills, or other indicators) and apply interventions *as deemed appropriate* (PA for further fills, patient or prescriber letters, "lock in," continued monitoring, etc.).

2. Prospective safety edits and claims review automated process on quantity dispensed for initial and subsequent fills to minimize potential for inappropriate use and diversion

CCOs must apply prospective safety edits (such as PA review) to limit quantities of dispensed pills and to dose optimize when clinically appropriate to minimize the risk of inappropriate use and diversion. For example, dose optimization may be required for patients receiving long-acting opioids, and this requirement may be applied through prior authorization review.

Periodic claims review to look for concerning treatment (could include claims with

[1] CMS Guidance defines "safety edits" as prospective drug review, such as is defined in § 1927(g)(2)(A) of the Social Security Act

[2] CMS Guidance defines "claims review automated process" as retrospective drug use review, such as is defined in § 1927(g)(2)(B) of the Social Security Act

quantities larger than typical FDA-labeled doses, quantities in excess of expected use for the probable indication, or quantities that are statistical outliers compared to similar patients prescribed opioids) and apply interventions *as deemed appropriate.*

3. Prospective safety edits and claims review automated process for therapeutically-duplicative initial and subsequent opioid prescription fills

CCOs must apply a point-of-sale alert ("soft edit" or "hard edit") that requires pharmacist or prescriber review when the claims system detects clinically significant overlapping opioid treatment. Alert must be overridable so there is minimal interference with appropriate therapy, such as through NCPDP DUR/PPS codes or through MCE or PBM review and authorization.

Periodic claims review to look for concerning treatment (could include patients with concurrent prescriptions for more than one type of opioid [short and long-acting opioids or use of multiple molecular entities] or patients with concurrent opioid prescriptions from multiple providers) and apply interventions as deemed appropriate.

4. Prospective safety edits and claims review automated process for a state-defined maximum daily morphine equivalent for treatment of chronic pain

90 morphine equivalents daily (MED) for at least short acting opioids, applied at least to individual prescriptions and enforced by prior authorization, quantity limits, or "soft edits" at point-of-sale. Edits must apply to initial refills and refills, though method of enforcement may differ.

Periodic claims review to look for concerning treatment (could include high cumulative MED, rapid recent increase in MED, or other indicators) and apply interventions *as deemed appropriate* (patient or prescriber letters, "lock in," continued monitoring, etc.).

5. Claims review automated process that monitors when a client is concurrently prescribed opioids and benzodiazepines or antipsychotics

MCEs must use the "push" list of mental health carve out drug claims to identify concerning concomitant opioid/benzo or opioid/antipsychotic treatment, and apply interventions *as deemed appropriate* (PA further fills, patient or prescriber letters, "lock in," continued monitoring, etc.).

6. Prospective safety edits and claims review automated processes to identify when a patient is prescribed an opioid after a recent diagnosis of opioid use disorder (OUD) or a prescription used to treat OUD

MCEs must apply an automated point-of-sale edit or a manual opioid PA review process

to assess appropriate opioid use for patients being treated for OUD or who have a known recent diagnosis of OUD. This process must not interfere with OUD treatment and must not interfere with appropriate pain management for individuals with OUD.

Periodic claims review to look for concerning treatment (could include concomitant long-term opioid use in patients prescribed MAT, opioid prescriptions from multiple prescribers or in excess of state defined limits for patients with a diagnosis of OUD, multiple denied opioid prescriptions in patients with OUD) and apply interventions *as deemed appropriate*.

7. Edits or processes to identify when a patient may be at high risk of opioid overdose and should be considered for co-prescription or co-dispensing of an FDA-approved opioid antagonist/reversal agent (naloxone)

MCEs must apply either an automated point-of-sale pharmacy messaging edit or a regular retrospective review (at least quarterly) to identify members at high risk for opioid overdose who do not have a recent naloxone prescription. “High risk” must at least include patients receiving chronic high-dose opioid treatment and patients receiving high-risk concurrent treatment (such as concurrent long- and short-acting opioid, concurrent opioid a benzodiazepine, or concurrent buprenorphine for MAT and a controlled substance). Apply interventions to mitigate overdose risk, ensure access to naloxone, and increase care coordination between the member, pharmacy, and prescriber as clinically indicated.

8. Program to monitor and manage the appropriate use of antipsychotic medications by Medicaid children. [Handled by OHA, no additional CCO action required]

Handled by OHA as follows:

- **Non-foster care:** Periodic claims review with referral for specialist consultation when concerning treatment is identified (e.g., long-term antipsychotic use in patients < 10 years of age).
- **Foster care:** Yearly review of foster-care children prescribed mental health medications. If concerning treatment is identified, providers are referred for consultation with a specialist. Examples of concerning treatment may include patients <18 years of age prescribed antipsychotics, prescription of an antipsychotic without diabetic screening, prescription of three or more psychotropics, patients with no documented age-appropriate indication for therapy, or children prescribed a psychotropic not FDA-indicated for children.

9. Process that “identifies potential fraud or abuse of controlled substances” by Medicaid clients, enrolled prescribers, and enrolled dispensing pharmacies

Periodic claims review to look for potential fraud or abuse of controlled substances by clients, prescribers and pharmacies (could include clients filling prescriptions at multiple pharmacies, prescribers or pharmacies filling high volumes of controlled substances, or other indicators) and interventions *as deemed appropriate* (lock-in, PDMP assessment,

peer-to-peer consultation, etc.)

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OHSU Drug Effectiveness Review Project Summary Report – Second Generation Antipsychotic Medications in Children and Adolescents

Date of Review: April 2021

Date of Last Review: August 2020 (Adults/Pediatrics)
Literature Search: 01/01/1946-04/14/2020

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

Research Questions:

1. What are the benefits and harms of using second generation antipsychotics (SGAs) to treat adolescents with schizophrenia and other psychotic disorders, first episode schizophrenia, and bipolar disorder?
2. What are the benefits and harms of using SGAs to treat children and adolescents with agitation associated with autism spectrum disorder (ASD)?
3. What are the benefits and harms of using SGAs to treat children and adolescents with disruptive behavior disorders, impulse control disorders, and conduct disorders?

Conclusions:

- Irritability Associated with Autism Spectrum Disorder
  - Fourteen randomized controlled trials (RCTs) were included in the analysis.
  - Agents studied included: aripiprazole, lurasidone, and risperidone.
  - Risperidone and aripiprazole demonstrated efficacy using the Aberrant Behavior Checklist and Clinical Global Impressions-Improvement subscale, lurasidone did not.
  - Most Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) outcome ratings were moderate given larger sample sizes than seen in other therapeutic areas.
  - Most studies were placebo-controlled.
- Schizophrenia and First Episode Psychosis
  - Sixteen RCTs were included in the analysis.
  - Agents studied included: aripiprazole, asenapine, haloperidol (not SGA), lurasidone, molindone (not available in United States), olanzapine, paliperidone extended release (ER), quetiapine, and risperidone.
  - No head-to-head studies showed statistical improvement of one therapy over another, though all drugs did show benefit over placebo for symptomatic and functional improvement using various assessment scales.
  - Most studies had moderate or high risk of bias, and many studies had high placebo response rates.

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- Most GRADE outcome ratings were low to very low.
- Patients with first episode psychosis may be more sensitive to adverse events (AEs), particularly weight gain, than patients who have used antipsychotics in the past.

- Bipolar Disorder
  - Ten RCTs were included in the analysis.
  - Agents studied included: aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, quetiapine extended release (XR), and risperidone.
  - Six of the 10 RCTs were 4 weeks or less, which may be inadequate to determining full response to treatment.
  - All trials were placebo controlled except for one head-to-head study of risperidone vs. quetiapine in bipolar II depression.
  - SGAs lowered patient scores on mania assessments versus placebo. A Young Mania Rating Scale and/or Clinical Global Impressions-Improvement score indicating moderate to severe disease were common patient inclusion critera.
  - SGAs did not provide greater benefit than placebo in patients with bipolar depression (bipolar I or bipolar II) based on Children's Depression Rating Scale and Clinical Global Impressions-Bipolar Disorder assessment.
  - GRADE ratings were low to very low, with improvement on the Young Mania Rating Scale for asenapine over placebo rated as moderate.
- Disruptive Behavior Disorders
  - Eight RCTs were included in the analysis.
  - Agents studied included: aripiprazole, quetiapine, and risperidone.
  - Head-to-head studie of risperidone versus aripiprazole showed no statistical improvement of one therapy over another.
  - Risperidone consistently showed functional and symptomatic outcome improvements when given according to typical clinical dosage.
  - Risperidone demonstrated efficacy soon after treatment initiation (2 weeks).
  - GRADE ratings ranged from moderate to very low. All efficacy outcomes for quetiapine were considered very low because of small sample size.
- Harms
  - Weight gain is a common AE with SGAs, and typically increases with longer treatment exposure.
  - Prolactin levels often increase with risperidone and paliperidone ER, and may decrease with aripiprazole.
  - Electrocardiogram (ECG) changes were not routinely reported.
  - Akathisia and extrapyramidal symptoms (EPS) are increased with all SGAs compared to placebo. Risperidone, aripiprazole, paliperidone ER, lurasidone, and asenapine may have highest risk.
  - Other metabolic parameters (total cholesterol, low-density lipoprotein [LDL], triglycerides, and fasting glucose) should be monitored for all SGAs, particularly olanzapine and quetiapine.
  - Elevations in liver enzymes resulted in study discontinuation in multiple patients with schizophrenia taking olanzapine in a single study.
  - Grade ratings were not included for harms outcomes in this review, consider evidence insufficient.
- There is lack of evidence testing for the effectiveness of SGAs in improving school progress.
- Hospitalizations, need for acute symptom treatment, and progress in different social settings (such as school) were not discussed in these studies in relation to ASD and disruptive behavior disorder.

Recommendations:

- No changes to current preferred drug list (PDL).
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

In the Oregon Health Plan, antipsychotic drugs (APD) are exempt from traditional preferred drug list (PDL) and prior authorization (PA) requirements. However, clinical PA criteria that address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use. The PA criteria for the quetiapine safety edit is outlined in **Appendix 2**. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone palmitate, and risperidone are on the PDL. Oral SGAs on the PDL are listed in **Appendix 1**. Most APD use in the Oregon Medicaid population is for oral SGAs, including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of APD claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable APDs in this class. Overall, oral and parenteral SGAs represent some of the highest gross expenditure on the PDL. Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania, or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high-quality systematic reviews to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other APDs.

Methods:

The September 2020 drug class report on Second Generation Antipsychotic Medications in Children and Adolescents by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

PICOS

The population for this report included individuals with diagnosis as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (preferred) or investigator-defined criteria for diagnosis in the absence of DSM-5 criteria. These included:

- Adolescents (12-17 years) with a diagnosis of schizophrenia or other psychotic disorder, such as schizophreniform disorder (<6 months duration of schizophrenia symptoms), delusional and schizoaffective disorders, first episode schizophrenia, and patients who are refractory to treatment.
- Adolescents (12-17 years) and children (under 12 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states).
- Adolescents (12-17 years) or children (under 12 years) with DSM-5 diagnosis of ASD.
- Adolescents (12-17 years) children (under 12 years) with a DSM-5 diagnosis of disruptive behavior, impulse control, or conduct disorders.

The medications with FDA approval for use in children and adolescents and included in this review are available in **Appendix 3**. The review searched for head-to-head comparisons and placebo comparisons for all populations. Study designs were limited to RCTs. Quality of life, functional capacity, hospitalization, persistence (ability to continue medication over time) and symptom response were the efficacy and effectiveness outcomes, while harms included overall AEs, withdrawals due to AEs, and specific adverse events. There were 22 different rating scales included in outcomes throughout the report, with the most common being the Aberrant Behavior Checklist (ABC), Clinical Global Impressions (CGI with Severity and Improvement subscales), Nisonger Child Behavior Rating Form (NCBRF), Postive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale-Child (BPRS-C), Children's Global Assessment Scale (CGAS), Young Mania Rating Scale (YMRS), Children's Depression Rating Scale-Revised Version (CDRS-R), and Conners Parent Rating Scale (CPRS).

A total of 60 publications, representing 48 RCTs, met criteria and were included in the data synthesis.

Summary Findings:
This report did not include a pooled meta-analysis of study outcomes given small number of trials with similar endpoints and comparison groups. Therefore, an overall quantitative assessment with magnitude of effect is not available.

Irritability in ASD

There were 14 RCTs analyzed which included an intervention for irritability in patients with ASD or developmental disorders. Most of the studies focused on participants aged 5 to 17, while 1 study focused specifically on preschool aged children. Patients generally had a baseline Abberant Behavior Checklist-Irritability (ABC-I) of 18 or more, indicating moderate to severe agitation. The studies were rated as low risk of bias (RoB) (5 studies), moderate RoB (6 studies), and high RoB (3 studies), with the most common limitations being small sample sizes (range 23 to 316 participants), high attrition rates, and significant involvement of industry beyond study funding. Details of efficacy outcomes are provided in **Table 1.** Most studies lasted 8 to 16 weeks.

Table 1: Efficacy outcomes for Irritability Associated with ASD

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
ABC-I	Risperidone vs. placebo 3 RCTs; N=331	Moderate Downgraded 1 level for risk of bias	Risperidone superior to placebo
	Risperidone vs. aripiprazole 2 RCTs; N=120	Moderate Downgraded 1 level for risk of bias	Risperidone was similar to aripiprazole
	Aripiprazole vs. placebo 4 RCTs; N=493	Moderate Downgraded 1 level each for risk of bias and inconsistency Upgraded 1 level for aripiprazole dose-response relationship	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate Downgraded 1 level for imprecision	Lurasidone was not efficacious compared to placebo
CGI-I	Risperidone vs. placebo 2 RCTs; N=197	Moderate Downgraded 1 level for risk of bias	High-dose risperidone may have better efficacy than placebo
	Risperidone vs. aripiprazole 2 RCTs; N=120	Moderate Downgraded 1 level for risk of bias	Risperidone was similar to aripiprazole
	Aripiprazole vs. placebo 4 RCTs; N=493	Moderate Downgraded 1 level for risk of bias Upgraded 1 level for aripiprazole dose-response relationship	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate Downgraded 1 level for inconsistency	Uncertain relationship between lurasidone and placebo Low dose showed significant improvement while high dose did not
CGI-S	Risperidone vs. placebo 3 RCTs; N=258	Moderate Downgraded 1 level for risk of bias	No significant difference between risperidone and placebo
	Aripiprazole vs. placebo 3 RCTs; N=408	Moderate Downgraded 1 level for risk of bias	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate No downgrading or upgrading for this outcome	Lurasidone was similar to placebo
NCBRF-Conduct Problem	Risperidone vs. placebo 2 RCTs; N=134	Moderate Downgraded 1 level for risk of bias	Risperidone was superior to placebo

Abbreviations: ABC-I = Aberrant Behavior Checklist-Irritability domain; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; NCBRF = Nisonger Child Behavior Rating Form; RCTs = randomized controlled trials.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Schizophrenia and First Episode Psychosis

There were 16 RCTs analyzed for schizophrenia and first episode psychosis. The studies were rated as low RoB (1 study), moderate RoB (7 studies), and high RoB (8 studies). Details of efficacy outcomes are provided in **Table 2.** Studies had 22 to 326 participants with most frequent duration of 6 to 12 weeks, and a range of 6 to 52 weeks for schizophrenia and 6 weeks to 6 months for first episode psychosis.

Table 2: Efficacy Outcomes for Schizophrenia

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
Schizophrenia			
PANSS Total score	Risperidone vs. olanzapine: 3 RCTs; N = 171	Low Downgraded 1 level for risk of bias and 1 level for indirectness	No significant difference was observed between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Low Downgraded 1 level for risk of bias and 1 level for imprecision	Risperidone was superior to quetiapine.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	High-dose aripiprazole was more efficacious than placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Very low Downgraded 2 levels for risk of bias and 1 level for inconsistency	Uncertain relationship between paliperidone and placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Low Downgraded 2 levels for risk of bias	Quetiapine was superior to placebo.
	Paliperidone vs. aripiprazole: 1 RCT; N = 228	Low Downgraded 2 levels for risk of bias	No difference between paliperidone and aripiprazole.
	Asenapine vs. placebo: 1 RCT; N = 306	Moderate Downgraded 1 level for risk of bias	No difference between asenapine and placebo.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
CGI-S Score	Risperidone vs. olanzapine: 3 RCTs; N = 106	Low Downgraded 1 level for risk of bias and 1 level for indirectness	No significant differences were observed between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Very low	No significant differences between risperidone and quetiapine.

		Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for imprecision	
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	Both low and high doses of aripiprazole were statistically significantly superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Low Downgraded 2 levels for risk of bias	Both medium and high paliperidone doses were more effective compared to placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Low Downgraded 2 levels for risk of bias	High-dose quetiapine was statistically significantly superior to placebo.
	Paliperidone vs. aripiprazole: 1 RCT; N = 228	Low Downgraded 2 levels for risk of bias	No difference between paliperidone and aripiprazole.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
CGAS Score	Risperidone vs. olanzapine: 2 RCTs; N = 55	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between risperidone and quetiapine.
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	Both low and high doses of aripiprazole were statistically significantly superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Low Downgraded 2 levels for risk of bias	Uncertain relationship between paliperidone and placebo; mixed results.
	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
	Risperidone vs. olanzapine vs. molindone:	Moderate Downgraded 1 level for risk of bias	Both risperidone and olanzapine had better efficacy than placebo.

	1 RCT; N = 116		
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
BPRS-C	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
First Episode Psychosis			
PANSS	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No difference between quetiapine and risperidone.
	Quetiapine vs. aripiprazole: 1 RCT; N = 113	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and aripiprazole.
CGI-S Score	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No difference between quetiapine and risperidone.
CGAS Score	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.

Abbreviations: BPRS-C = Brief Psychiatric Rating Scale-Child; CGAS = Children's Global Assessment; CGI-S = Clinical Global Impressions Scale- Severity; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PANSS = Positive and Negative Syndrome Scale; N = number; RCT = Randomized controlled trial.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Bipolar Disorder

There were 10 RCTs analyzed for bipolar affective disorder included in this review. The studies were rated as low RoB (1 study), moderate RoB (3 studies), and high RoB (6 studies). Details of efficacy outcomes are provided in **Table 3.** Studies had 22 to 403 participants with most frequent duration of 3 to 8 weeks, and a range of 3 to 72 weeks. Only one study included head-to-head comparison of two drugs (quetiapine vs. risperidone); this 12-week, open-label trial was the smallest of the analysis.

Table 3: Efficacy Outcomes for Bipolar Disorder

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
YMRS	Olanzapine vs. placebo: 1 RCT; N = 161	Low Downgraded 2 levels for risk of bias	Olanzapine was statistically superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 169	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Risperidone was statistically superior to placebo.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for imprecision	No significant difference between quetiapine and risperidone.
	Quetiapine vs. placebo: 1 RCT; N = 316	Low Downgraded 2 levels for risk of bias	No significant difference between quetiapine and placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 296	Low Downgraded 2 levels for risk of bias	Aripiprazole was statistically superior to placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level of risk of bias	Asenapine was statistically superior compared to placebo.
CDRS-R	Quetiapine vs. placebo: 3 RCTs; N = 509	Very low Downgraded 2 levels for risk of bias and 1 level for inconsistency	No significant difference was observed between quetiapine and placebo. High-dose quetiapine may have some efficacy over placebo.
	Aripiprazole vs. placebo: 2 RCTs; N = 356	Low Downgraded 2 levels for risk of bias	No difference between aripiprazole and placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level for risk of bias	No difference between asenapine and placebo.
	Lurasidone vs. placebo: 1 RCT; N = 347	Moderate Downgraded 1 level for risk of bias	Lurasidone was statistically superior to placebo.
CGAS Score	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between quetiapine and risperidone.
	Quetiapine vs. placebo: 1 RCT; N = 284	Low Downgraded 2 levels for risk of bias	Both quetiapine doses were statistically superior to placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 296	Low Downgraded 2 levels for risk of bias	Aripiprazole was statistically superior to placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level for risk of bias	Asenapine was statistically superior to placebo.

Abbreviations: CDRS-S = Children's Depression Rating Scale-Revised Version; CGAS = Children's Global Assessment Scale; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; RCT = randomized controlled trial; YMRS = Young Mania Rating Scale.

*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Disruptive Behavior, Impulse Control, and Conduct Disorders

Eight RCTs were identified and analyzed for disruptive behavior, impulse control, and conduct disorders in this review. The studies were rated as moderate RoB (4 studies) and high RoB (4 studies). Details of efficacy outcomes are provided in **Table 4**. One study assessing risperidone versus placebo was significantly larger (N=335) and longer (6 months) than the other trials, which included 13 to 118 participants and had durations of 4 to 10 weeks. Most studies allowed or required sub-average intelligence quotient for study enrollment.

Table 4: Efficacy Outcomes for Disruptive Behavior, Impulse Control, and Conduct Disorders

Outcome	**Comparison**	**Quality of Evidence (GRADE)**	**Evidence conclusion***
N-CBRF Conduct Subscale	Risperidone vs. placebo: 4 RCTs; N = 640	Moderate Downgraded 1 level for risk of bias	Statistically significant improvement in risperidone group compared to placebo.
VAS	Risperidone vs. placebo: 5 RCTs; N = 653	Moderate Downgraded 1 levels for risk of bias	Risperidone was superior to placebo.
CGI-I	Risperidone vs. placebo: 3 RCTs; N = 248	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Low Downgraded 2 levels for risk of bias	No difference between risperidone and aripiprazole.
CGI-S	Risperidone vs. placebo: 2 RCTs; N = 355	Low Downgraded 2 levels for risk of bias	The relationship between risperidone and placebo was uncertain. One trial demonstrated significance and one did not.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Very low Downgraded 2 levels for risk of bias and 1 for imprecision	No difference between risperidone and aripiprazole.
	Quetiapine vs. placebo: 1 RCT; N = 19	Very low Downgraded 2 levels for risk of bias and 1 for imprecision	Quetiapine was statistically significant over placebo by week 5 (total 7 week duration)
ABC-I	Risperidone vs. placebo: 3 RCTs; N = 241	Low Downgraded 2 levels for risk of bias	Statistically significant improvement in risperidone group compared to placebo.
CPRS	Risperidone vs. placebo: 1 RCT; N = 20	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Risperidone had some efficacy over placebo.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	No difference between risperidone and aripiprazole.
	Quetiapine vs. placebo: 1 RCT; N = 19	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Unable to detect differences between the experimental and control group for CPRS-CP due to small sample size.

Abbreviations: ABC = Aberrant Behavior Checklist-irritability subscale; CGI-I = Clinical Global Impressions-improvement; CGI-S = Clinical Global Impressions-severity; CPRS = Conners Parent Rating Scale; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; N-CBRF = Nisonger Child Behavior Rating Form; RCT = randomized controlled trial; VAS = Visual Analog Scale.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Harms

Harms data varied in assessment and may be affected by length of intervention, with longer studies more likely to reveal certain side effects. Harms were not pooled between studies in this report and there are no GRADE ratings.

ASD

In general, weight gain (2.7 to 5.7 kg), drowsiness/somnolence, increased prolactin, and fatigue were all more common in risperidone treated patients, while no change was noted in ECG measures. No significant differences were noted in lipid measures, fasting plasma glucose, or abnormal involuntary movement scale (AIMS) measures, though maximum trial duration of 16 weeks may have limited these outcomes. An increased appetite and EPS were noted in some studies.

Aripiprazole was also associated with weight gain (1.3 to 11 kg), somnolence, fatigue, EPS, and drooling. Weight differences were not always statistically significant versus placebo. Changes in appetite and ECG were not noted. Decreased prolactin was noted in more than one study.

Lurasidone patients had higher rates of vomiting and somnolence, as well as weight gain (0.5 to 1.2 kg, dose dependent) than placebo.

Adverse event rates of interest, such as movement-related AEs and metabolic parameters were not reported in all studies.

Schizophrenia and First Episode Psychosis

Olanzapine was associated with significant, non-time limited weight gain. Olanzapine and quetiapine increased other metabolic parameters, including: total cholesterol, LDL, triglycerides, and fasting blood glucose. Prolactin was increased with risperidone and paliperidone ER, but decreased with aripiprazole. All SGAs tested in this population were associated with increased akathisia and EPS compared to placebo, with risperidone, aripiprazole, paliperidone ER, lurasidone, and asenapine being associated with the highest risk.

Bipolar Disorder

Six of the 10 trials involving patients with bipolar disorder were 4 weeks or less in duration, making assessment of long-term side effects more difficult. Olanzapine, then quetiapine and risperidone caused the greatest weight gain. Similar to patients with schizophrenia, risperidone increased prolactin while aripiprazole decreased the prolactin level. Weight gain for asenapine versus placebo varied by trial.

Disruptive Behavior, Impulse Control, and Conduct Disorders

Description of AEs in patients with these diagnoses were difficult. High rates of AEs in both active and placebo groups were reported, and differentiation of AEs from symptoms associated with underlying condition was challenging. Weight gain was noted and tended to increase with longer exposure. Clinical effects of

increased prolactin concentrations with risperidone use were not seen in these short-term studies. Extrapyramidal symptoms and abnormal movements were not commonly reported.

Ongoing Trials

There are two ongoing trials, both for ASD, that fit within the scope of this review. A single phase 2 RCT is evaluating risperidone vs. placebo in 8 to 16-year-olds, while a phase 3 RCT compares aripiprazole vs. placebo in 6 to 17-year-olds. Data completion is estimated for December 1, 2016 for 41 patients for the phase 2 trial, and April 1, 2020 with an enrollment of 100 patients in the aripiprazole study.

References:

1. Drug Effectiveness Review Project (DERP). Second Generation Antipsychotic Medications in Children and Adolescents: Systematic Review Update. September 2020

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
aripiprazole	ABILIFY	ORAL	TABLET	Y
aripiprazole	ARIPIPRAZOLE	ORAL	TABLET	Y
asenapine maleate	ASENAPINE MALEATE	SUBLINGUAL	TAB SUBL	Y
asenapine maleate	SAPHRIS	SUBLINGUAL	TAB SUBL	Y
cariprazine HCl	VRAYLAR	ORAL	CAP DS PK	Y
cariprazine HCl	VRAYLAR	ORAL	CAPSULE	Y
clozapine	CLOZAPINE	ORAL	TABLET	Y
clozapine	CLOZARIL	ORAL	TABLET	Y
lurasidone HCl	LATUDA	ORAL	TABLET	Y
olanzapine	OLANZAPINE	ORAL	TABLET	Y
olanzapine	ZYPREXA	ORAL	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	ORAL	TABLET	Y
quetiapine fumarate	SEROQUEL	ORAL	TABLET	Y
risperidone	RISPERDAL	ORAL	SOLUTION	Y
risperidone	RISPERIDONE	ORAL	SOLUTION	Y
risperidone	RISPERDAL	ORAL	TABLET	Y
risperidone	RISPERIDONE	ORAL	TABLET	Y
ziprasidone HCl	GEODON	ORAL	CAPSULE	Y
ziprasidone HCl	ZIPRASIDONE HCL	ORAL	CAPSULE	Y
aripiprazole	ARIPIPRAZOLE	ORAL	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	ORAL	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	ORAL	TAB SENSPT	V
asenapine	SECUADO	TRANSDERM	PATCH TD24	V
brexpiprazole	REXULTI	ORAL	TABLET	V
clozapine	VERSACLOZ	ORAL	ORAL SUSP	V
clozapine	CLOZAPINE ODT	ORAL	TAB RAPDIS	V
clozapine	FAZACLO	ORAL	TAB RAPDIS	V
iloperidone	FANAPT	ORAL	TAB DS PK	V
iloperidone	FANAPT	ORAL	TABLET	V
lumateperone tosylate	CAPLYTA	ORAL	CAPSULE	V
olanzapine	OLANZAPINE ODT	ORAL	TAB RAPDIS	V
olanzapine	ZYPREXA ZYDIS	ORAL	TAB RAPDIS	V
paliperidone	INVEGA	ORAL	TAB ER 24	V

paliperidone	PALIPERIDONE ER	ORAL	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	ORAL	CAPSULE	V
pimavanserin tartrate	NUPLAZID	ORAL	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	ORAL	TAB RAPDIS	V

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	

Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *4/21(SF); 8/20 (SF); 3/19 (DM); 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Appendix 3: Medications Included

Generic Name	Brand Name	Form	Initial Year Approved	Approved Indications in Children[b] or Adolescents[a]
Aripiprazole	Abilify	Oral tablet	2002	Schizophrenia[a] Bipolar disorder[a,b] ASD[a,b]
Asenipine	Saphris	Sublingual tablet	2009	Bipolar disorder[a]
Lurasidone	Latuda	Oral tablet	2010	Schizophrenia[a] Bipolar disorder[a,b]
Olanzapine	Zyprexa	Oral tablet	1996	Schizophrenia[a] Bipolar disorder[a]
	Zyprexa Zydis	ODT	2000	
Paliperidone	Invega	ER oral tablet	2006	Schizophrenia[a]
Quetiapine	Seroquel	Oral tablet	1997	Schizophrenia[a] Bipolar disorder[a,b]
	Seroquel XR	ER oral tablet	2007	
Risperidone	Risperdal	Oral tablet	1993	Schizophrenia[a] Bipolar disorder[a,b] ASD[a,b]
		Oral solution	1996	
	Risperdal M-TAB	ODT	2003	

Abbreviations. ASD: autism spectrum disorder; ER: extended release; ODT: orally disintegrating tablet; XR: extended release.

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Drug Use Evaluation: Combination Therapy with Antipsychotics and Other Psychotropic Drugs

Research Questions:

1. How frequently are Medicaid patients prescribed an antipsychotic in combination with another psychotropic drug? Are there age groups (e.g., children, adolescents, or adults) in which combination prescribing is more frequent?
2. How many patients are prescribed ongoing long-term combination therapy?
3. What providers commonly prescribe combination stimulants and antipsychotics?
4. What are common diagnoses for patients prescribed combination stimulants and antipsychotics?

Conclusions:

1. Frequency of combination therapy
    - Of the 29,460 patients identified with claims for an antipsychotic in 2018, 37% (n=10,989) had combination use of at least one other mental health drug. This included 738 children, 938 adolescents, and 9,313 adults.
    - The most common concurrent drug therapy included antipsychotics in combination with antidepressants (84%), benzodiazepines (17%), and stimulants (13%).
    - About 2% of all patients had claims for 5 or more mental health drugs for more than 90 days (n=237).
2. Proportion of patients with long-term combination therapy
    - More than 75% of patients with at least 90 days of concomitant therapy were likely to continue use of combination therapy beyond 150 days.
3. Prescriber characteristics of stimulant and antipsychotic co-prescribing
    - Antipsychotics were most commonly prescribed from specialists (including mental health nurse practitioners and psychiatrists).
    - In only 55% of patients, antipsychotics and stimulants were prescribed from the same provider.
4. Diagnostic characteristics of stimulant and antipsychotic co-prescribing
    - The most common indications identified via medical claims in patients prescribed antipsychotics in combination with stimulants included depression (35%), bipolar disorder (26%), autism (20%) and conduct disorder (20%). ADHD was diagnosed in 81% of patients.
    - Twenty-one percent of patient did not have an identified FDA-approved indication for antipsychotics, and 16% of patients did not have an identified indication for stimulant based on analysis of their medical claims. Other common diagnoses in this population included severe stress reactions/adjustment disorders, anxiety disorders, disorders of abuse and dependence (including opioid, alcohol, and cannabis), eating disorders (including anorexia), and other developmental or personality disorders.
    - Diagnoses related to box warnings of antipsychotics or stimulants were infrequent and most commonly pertained to suicidal ideation or suicide attempts (n=127; 9%). Diagnoses of stimulant abuse was identified in 59 patients (4%) prescribed combination antipsychotics and stimulants.

Recommendations:
Review profiles of patients with the following high risk categories to identify opportunities for therapy optimization or de-prescribing:

- Patients with long-term use (>90 days) of 6 or more mental health drugs (or >4 drugs in children)
- Patients with possible contraindications to therapy for antipsychotics and stimulants (such as elderly patients with dementia-related psychosis and stimulant abuse)
- Children without FDA-approved diagnoses or claims history indicating use of non-pharmacological psychosocial services
- Children less than 5 years of age prescribed a stimulant or antipsychotic

Background
Often patients with multiple chronic conditions have an associated increased risk of drug adverse events, polypharmacy, decreased quality of life and greater use of healthcare services. Use of multiple medications can be appropriate to manage patient symptoms and prevent disease progression. However, use of multiple medications can also lead to increased risk of adverse effects and drug-drug interactions. Polypharmacy becomes inappropriate when risk of adverse events outweigh medication benefits. Though definitions in the literature can vary, polypharmacy is most commonly defined as use of 5 or more concomitant medications. The 2018 Scottish Government Polypharmacy Model of Care Group, provide guidelines to identify the patients at highest risk of harm due to polypharmacy and propose approaches to improve outcomes for patients.[1] Patients at highest risk for inappropriate polypharmacy are those with greatest frailty (e.g., elderly or those in resident care homes), those on more medications (≥10 drugs), and those taking high-risk medications or risky combinations of medications (e.g, anticholinergics or sedating medications).[1] Current programs which examine polypharmacy in the fee-for-service Medicaid program focus on patients prescribed more than 15 medications.

Many classes of medications for mental health conditions are associated with anticholinergic effects or central nervous system depression, and risk of adverse effects can increase with concomitant use of multiple drugs. Additional drug-disease interactions can occur for patients prescribed stimulants and antipsychotics. For example, current labeling for many stimulants includes warnings and precautions for psychiatric adverse reactions.[2] Exacerbation of pre-existing psychosis, induction of maniac episodes in patients with bipolar disorder, and new psychotic or maniac symptoms have been documented in patients prescribed drugs to treat ADHD such as methylphenidate or atomoxetine.[2,3] Stimulant discontinuation should be considered in patients who experience new or worsening hallucinations, delusions, or mania. Because events are primarily derived from post-marketing reports the exact incidence of psychiatric adverse reactions is unknown. Additionally antipsychotics and stimulants may have opposing effects and use of antipsychotics in conjunction with stimulant medications may decrease stimulant efficacy.[4] Monitoring for efficacy and adverse events is recommended when these agents are used in conjunction. For patients with comorbid ADHD experiencing an acute psychotic or maniac episode, guidelines from NICE recommend discontinuation of any ADHD medication with re-initiation of therapy only after the episode has resolved and after re-assessment of risks and benefits of ADHD treatment.[5] In adults with ADHD and comorbid aggression, rages or irritability the use of combination stimulants and antipsychotic therapy is not recommended.[5] No adjustments to ADHD drug regimen are recommended for patients with comorbid anxiety disorder, tic disorder or autism spectrum disorder.[5] Slower dose titration and more frequent monitoring is recommended for stimulant use in patients with comorbid mental health conditions including schizophrenia, bipolar disorder, and depression.[5]

In children and adolescents especially, the evidence supporting efficacy of combination psychotropic medications or antipsychotics is limited. Primary first-line therapy for many psychiatric conditions in children focuses on non-pharmacological treatment. Pharmacotherapy use in children or adolescents is typically only recommended in conjunction with an assessment and recommendation from a child and adolescent psychiatrist. **Table 1** lists current NICE recommendations for pharmacotherapy in children and adolescents with mental health conditions. In all cases, use of antipsychotics in children requires frequent reassessment to evaluate treatment efficacy and monitoring for adverse effects.

Table 1. NICE guidance for treatment of mental health conditions in children and adolescents.

Condition	Involvement of child mental health specialists in prescribing	Recommendation for pharmacotherapy
Psychosis or schizophrenia[6]	Consult upon initiation of any antipsychotic.	- Do not use antipsychotics unless there are sufficient symptoms to definitively diagnose psychosis or schizophrenia. - Use antipsychotics only in conjunction with psychological interventions such as CBT.
Bipolar Disorder[7]	Consult with diagnosis of any patients younger than 14 years of age.	- Antipsychotic therapy may be considered to treat mania, hypomania, or moderate to severe depressive symptoms, but is not routinely recommended for longer than 12 weeks.
Depression[8]	Consult upon initiation of pharmacotherapy. A second consultation is recommended before initiation of second-line antidepressant therapy.	- Pharmacotherapy should be considered only after trial and failure of psychosocial therapy. - Fluoxetine is the recommended first-line agent. - Citalopram or sertraline is recommended as a second-line option.
Autism[9]	Consult with pediatrician or psychiatrist upon initiation of pharmacotherapy	- Pharmacotherapy is not routinely recommended. - Antipsychotics are recommended only with severe behavior non-responsive to psychosocial therapy. - Treatment discontinuation is recommended within 6 weeks if efficacy is not established
ADHD[5]	Consult with 2 specialists before use of ADHD drugs in children under 5 years of age.	- Pharmacotherapy is not routinely recommended for children under 5 years of age. - In patients over 5 years of age, ADHD drugs are recommended only with patient and parental education and if ongoing symptoms are present after trial of environmental modifications. - Reassess ongoing need of ADHD drugs at least yearly.
Conduct Disorder or oppositional defiant disorder[10]	Consult upon initiation of risperidone	- Routine use of pharmacotherapy is not recommended - Risperidone may be considered for short-term management of severely aggressive behavior - Treatment discontinuation is recommended within 6 weeks if efficacy is not established

Abbreviations: ADHD = attention deficit hyperactivity disorder; CBT = cognitive behavioral therapy

However, despite recommendations, use of multiple medications for mental health conditions is common in children. A recent review of Medicaid claims data from 4 states (California, New York, Illinois, Texas) identified that from 2003 to 2007 approximately 19% of children and adolescents prescribed a long-acting stimulant had concurrent use of a second-generation antipsychotic for at least 14 days.[11] The average length of concurrent utilization was 130 days (SD 98).[11] Similarly, concomitant use of antipsychotics and antidepressants is common as antipsychotics can be used to augment antidepressant therapy for treatment of depression. In another analysis of Medicaid data from 2004 to 2009 in 4 states (California, Florida, Illinois, New Jersey), approximately 43% of children and adolescents who were prescribed a second-generation antipsychotic had concomitant antidepressant use.[12] A similar proportion (43%) had concomitant stimulant and antipsychotic use.[12]

In Medicaid, several national quality metrics aim to improve use of psychotropic medications in children. Use of 2 concurrent antipsychotics for more than 90 days in children or adolescents is one of the Children's Health Care Quality Measures for Medicaid programs. On average, 3% of the Medicaid children and adolescents prescribed antipsychotics are prescribed more than one antipsychotic for longer than 90 days.[13] Similarly, a measure to evaluate the proportion of children and adolescents with use of first-line psychosocial care prior to use of an antipsychotic is included as part of these quality measures.[13] In Oregon Medicaid, several ongoing programs currently evaluate antipsychotic utilization in children. They include an annual profile review for foster care children prescribed mental health medications and provider consultation for children less than 10 years of age prescribed long-term antipsychotics. The goal of this drug use evaluation is to assess prescribing patterns for mental health medications in order to identify opportunities to improve and coordinate care for patients prescribed multiple medications.

Methods:
Included patients had a FFS claim for an antipsychotic (oral or injectable) from 1/1/18 to 12/31/18. The first FFS claim in the reporting period was classified as the index event (IE). Subgroup analyses were conducted for patients on concomitant psychotropic medications and concomitant stimulants for at least 90 days. Patients were excluded if they had Medicare Part D coverage or less than 75% of covered days in the 6 months before or after the IE. Baseline characteristics, including patient age, were assessed at the time of the IE.

The following definitions and categories were used for the analysis:

- New start patients were defined as patients without antipsychotic use in the 120 days prior to the IE.
- Prior history of antipsychotic use was evaluated in the 120 days prior to the IE.
- Adherence to antipsychotic therapy was estimated using the proportion of days covered (PDC) in the 6 months following the IE. PDC less than 25% may indicate only short-term therapy and PDC of >75% indicates long-term therapy. PDC of 25-75% may indicate therapy of medium duration, sporadic "as needed" therapy, or low adherence to long-term therapy.
- Diagnoses were identified using ICD-10 codes on medical claims in the 6 months before or after the IE (see **Appendix 1** for relevant ICD-10 codes).
- Combination therapy was defined as an overlapping period of an antipsychotic and other psychotropic medication for at least 90 days with no more than a 14 day gap in coverage. Combination use was assessed in the 6 months following the IE based on both FFS and CCO claims and stratified by PDL class (see **Appendix 1**). In patients with claims for ADHD drugs, therapy was categorized according to stimulant or non-stimulant use.
- Stimulants were defined as drugs in the Other Stimulant PDL class (modafinil, armodafinil, and solriamfetol) and stimulants in the ADHD drugs PDL class (amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamphetamine, methamphetamine, and methylphenidate).
- Duration of combination drug therapy was defined as the time to the first 14 day gap in combination drug use. The number of psychotropic drugs with overlapping therapy was identified based on the number of unique molecular entities or HSNs.
- Provider specialty was identified using the primary provider taxonomy.

Results:
Antipsychotic utilization

Table 2 describes characteristics for patients prescribed antipsychotics. Patients were primarily white adults. Approximately 14.5% of identified patients were children or adolescents. The majority of patients (93%) were prescribed a second generation antipsychotic and 63% had a history of antipsychotic use. About half of the identified patients had continued long-term antipsychotic use in the 6 months following the first identified claim.

Table 2. Baseline demographics for patients prescribed antipsychotics

	N=	29,460	%
Age			
Average (min - max)		36.4	(1-91)
0-4		42	0.1%
5-12		1,610	5.5%
13-18		2,627	8.9%
19-64		25,027	85.0%
65+		154	0.5%

Female	15,879	53.9%
Race		
White	17,250	58.6%
Native American	1,589	5.4%
Other	1,903	6.5%
Unknown	8,718	29.6%
Index Antipsychotic Class		
1st Gen	1,346	4.6%
2nd Gen	27,415	93.1%
Parenteral	699	2.4%
Prior Antipsychotic Use		
New start	10,766	36.5%
History of another antipsychotic	18,694	63.5%
Proportion of Days Covered in the 6 months following the IE		
>75%	15,636	53.1%
26-75%	9,221	31.3%
<=25%	4,603	15.6%

Subgroup analysis of combination antipsychotic therapy with other psychotropics

A subgroup analysis was conducted in patients with combination use of an antipsychotic and at least one other psychotropic drug for at least 90 days. Of the 29,460 patients identified with claims for an antipsychotic, 37% (n=10,989) had combination use of at least one other mental health drug (**Table 3**). The most common drug types included antidepressants (84%), benzodiazepines (17%), and stimulants (13%). The majority of prescriptions were for adult patients, though concomitant prescribing was identified in 738 children and 938 adolescents. Use of stimulants and non-stimulants for ADHD was more common in children and adolescents whereas antidepressant and benzodiazepine use was more common for adults. Because patients with Medicare were excluded from this population, only a small proportion of adults over 65 year of age were prescribed concomitant mental health drugs (n=79). About 2% of all patients had claims for 5 or more mental health drugs for more than 90 days (n=237). More than 75% of patients with at least 90 days of concomitant therapy were likely to continue use of combination therapy beyond 150 days. Duration of therapy was similar for all types of psychotropics (data not shown).

Table 3. Combination use of antipsychotics with other psychotropics stratified by age

	All		Age							
			0-12		13-18		19-64		>=65	
	#	%	#	%	#	%	#	%	#	%
Patients with >=90 day overlap by HSN	10,989		738		938		9,234		79	
Number of mental health drugs with >=90 day overlap by HSN (includes antipsychotics and psychotropics)										
2	6,890	62.7%	471	63.8%	560	59.7%	5,805	62.9%	54	68.4%
3	3,074	28.0%	193	26.2%	278	29.6%	2,584	28.0%	19	24.1%
4	901	8.2%	69	9.3%	79	8.4%	746	8.1%	7	8.9%
5	***203***	***1.8%***	8	1.1%	23	2.5%	171	1.9%	1	1.3%
≥6	***34***	***0.3%***	0	0.0%	3	0.3%	31	0.3%	0	0.0%
Patients with >=90 day overlap by Class	11,097		778		1,008		9,239		72	
Psychotropic drug type										
Antidepressant	9,329	84.1%	372	47.8%	717	71.1%	8,173	88.5%	67	93.1%
Benzodiazepine	1,826	16.5%	9	1.2%	38	3.8%	1,761	19.1%	18	25.0%
Stimulant (ADHD or other)	1,436	12.9%	411	52.8%	368	36.5%	657	7.1%	0	0.0%
ADHD non-stimulant	801	7.2%	305	39.2%	268	26.6%	228	2.5%	0	0.0%
Sedative	237	2.1%	0	0.0%	7	0.7%	230	2.5%	0	0.0%
Patients with concomitant use for more than 2 **antipsychotics** >90 days (based on HSN)	82	0.7%	0	0.0%	1	0.1%	80	0.9%	1	1.4%

Combination stimulant and antipsychotic use

Common indications associated with antipsychotic and stimulant use are shown in **Table 4**. Common indications identified via medical claims in patients prescribed antipsychotics in combination with stimulants included depression (35%), bipolar disorder (26%), autism (20%) and conduct disorder (20%). ADHD was diagnosed in 81% of patients. Twenty-one percent of patient did not have an identified indication for antipsychotics, and 16% of patients did not have an identified indication for stimulant based on analysis of their medical claims. However, other common mental health diagnoses present in this population which may be related to prescribing included severe stress reactions/adjustment disorders (such as PTSD), anxiety disorders, disorders of abuse and dependence (including opioid, alcohol, and cannabis), eating disorders (including anorexia), and other developmental or personality disorders. Diagnoses related to box warnings of antipsychotics or stimulants were infrequent and most commonly pertained to suicidal ideation or suicide attempts (n=127; 9%). Diagnoses of stimulant abuse was identified in only 59 patients (4%) prescribed combination antipsychotics and stimulants.

Table 4. Diagnoses in patients with combination stimulant and antipsychotic use. Patients with multiple diagnoses may be counted more than once.

	N	%
	1,436	
Antipsychotic FDA-Approved Indications	**1,127**	**78.5%**
Depression	500	34.8%
Bipolar Disorder	374	26.0%
Autism	293	20.4%
Conduct Disorder	293	20.4%
Other Psychotic Disorder*	133	9.3%
Schizophrenia	46	3.2%
Tourette Disorder	27	1.9%
None of the above	309	21.5%
Stimulant FDA-Approved Indications	**1,205**	**83.9%**
ADHD	1,164	81.1%
OSA	92	6.4%
Narcolepsy	14	1.0%
Binge Eating Disorder	12	0.8%
None of the above	231	16.1%
Diagnoses related to Black Box Warnings	**167**	**11.6%**
Suicidal ideation or suicide attempt	125	8.7%
Stimulant abuse	59	4.1%
Dementia-related psychoses	3	0.2%

* Includes Schizotypal, delusional, brief psychotic, shared psychotic, schizoaffective disorders, and other or unspecified psychotic disorders not due to a known substance or psychological condition. ¥The most frequent psychiatric diagnosis for patients prescribed stimulants and antipsychotics (top 20) was identified based on ICD-10 codes beginning with F and grouped by category using the first 3 characters of the ICD-10 code.

Prescribers associated with prescription of more than 1% of antipsychotics in patients with concomitant stimulant use are listed in **Table 5**. Antipsychotics were most commonly prescribed from specialists (including mental health nurse practitioners and psychiatrists). In about 55% of patients, antipsychotics and stimulants were prescribed from the same provider (**Table 6**). A small proportion of patients had 4 or more prescribers involved in prescribing stimulants and antipsychotics (n=87, 6%).

Table 5. Most common prescriber types for antipsychotic IE in patients with combination antipsychotic/stimulant use

Patients with overlapping antipsychotic and stimulant		**1,436**	**%**
#	Index Prescriber taxonomy		
1	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	479	33.4%
2	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	302	21.0%
3	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	194	13.5%
4	PHYSICIAN-PEDIATRICS	96	6.7%
5	PHYSICIAN-FAMILY MEDICINE	93	6.5%
6	NURSE PRACTITIONER - FAMILY	67	4.7%
7	PHYSICIAN-INTERNAL MEDICINE	27	1.9%
8	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS	25	1.7%
9	PHYSICIAN ASSISTANT	25	1.7%
10	PHYSICIAN ASSISTANT - MEDICAL	22	1.5%
11	NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	21	1.5%

Table 6. Number of prescribers involved in concomitant antipsychotic and stimulant therapy

Patients with overlapping antipsychotic and stimulant	**1,359**	**%**
Number of prescribers for combination therapy		
1	743	54.7%
2	359	26.4%
3	170	12.5%
4	59	4.3%
≥5	28	2.1%

Limitations:

Data presented in this report is based on Medicaid claims history that has several inherent limitations.

- Diagnostic accuracy: Diagnoses based on claims history may be inaccurate or incomplete. Because diagnoses are not associated with prescriptions, it is difficult to determine the intended indication for the drug, particularly when therapy is used off-label. Additionally, many patients in this analysis were enrolled in coordinated care organizations and delays in submission and processing of medical claims data may result is missed diagnoses.
- Provider specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified.

- Days of coverage: Estimates of covered days attempts to approximate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately. Days' supply submitted on claims (particularly injectable antipsychotics) may be inaccurate and estimates of PDC do not include medical claims.
- Definitions for new start patients: Prior use of mental health medications was only evaluated in the 120 days prior to the IE. Patients may have a remote history of antidepressant use beyond this date which could influence choice in current therapy.

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Appendix 1: Drug Coding

Table A1. Antipsychotic Drug Classes

Class	HSN	Generic
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001661	haloperidol lactate
Antipsychotics, 1st Gen	039886	loxapine
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001667	thiothixene HCl
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl
Antipsychotics, Parenteral	024551	aripiprazole
Antipsychotics, Parenteral	042595	aripiprazole lauroxil
Antipsychotics, Parenteral	045050	aripiprazole lauroxil,submicr.
Antipsychotics, Parenteral	001621	chlorpromazine HCl
Antipsychotics, Parenteral	001624	fluphenazine decanoate
Antipsychotics, Parenteral	001626	fluphenazine HCl
Antipsychotics, Parenteral	001660	haloperidol decanoate
Antipsychotics, Parenteral	001661	haloperidol lactate
Antipsychotics, Parenteral	011814	olanzapine
Antipsychotics, Parenteral	036716	olanzapine pamoate
Antipsychotics, Parenteral	036479	paliperidone palmitate
Antipsychotics, Parenteral	008721	risperidone
Antipsychotics, Parenteral	025509	risperidone microspheres
Antipsychotics, Parenteral	001630	trifluoperazine HCl
Antipsychotics, Parenteral	023379	ziprasidone mesylate

Table 2. Combination Psychotropic Drugs

Class	HSN	Generic
ADHD Drugs	043652	amphetamine
ADHD Drugs	002064	amphetamine sulfate
ADHD Drugs (non-stimulant)	024703	atomoxetine HCl
ADHD Drugs (non-stimulant)	000113	clonidine HCl
ADHD Drugs	022987	dexmethylphenidate HCl
ADHD Drugs	002065	dextroamphetamine sulfate
ADHD Drugs	013449	dextroamphetamine/amphetamine
ADHD Drugs (non-stimulant)	000120	guanfacine HCl
ADHD Drugs	034486	lisdexamfetamine dimesylate
ADHD Drugs	002067	methamphetamine HCl
ADHD Drugs	033556	methylphenidate
ADHD Drugs	001682	methylphenidate HCl
Antidepressants	001643	amitriptyline HCl
Antidepressants	001648	amoxapine
Antidepressants	045692	brexanolone
Antidepressants	036156	bupropion HBr
Antidepressants	001653	bupropion HCl
Antidepressants	010321	citalopram hydrobromide
Antidepressants	004744	clomipramine HCl
Antidepressants	001645	desipramine HCl
Antidepressants	040202	desvenlafaxine
Antidepressants	040692	desvenlafaxine fumarate
Antidepressants	035420	desvenlafaxine succinate
Antidepressants	001650	doxepin HCl
Antidepressants	026521	duloxetine HCl
Antidepressants	024022	escitalopram oxalate
Antidepressants	041003	esketamine HCl
Antidepressants	001655	fluoxetine HCl
Antidepressants	006338	fluvoxamine maleate
Antidepressants	001641	imipramine HCl
Antidepressants	001642	imipramine pamoate
Antidepressants	001638	isocarboxazid
Antidepressants	040632	levomilnacipran HCl
Antidepressants	001651	maprotiline HCl
Antidepressants	011505	mirtazapine
Antidepressants	009612	nefazodone HCl
Antidepressants	001644	nortriptyline HCl
Antidepressants	025800	olanzapine/fluoxetine HCl
Antidepressants	007344	paroxetine HCl
Antidepressants	025796	paroxetine mesylate
Antidepressants	001639	phenelzine sulfate
Antidepressants	001646	protriptyline HCl
Antidepressants	033510	selegiline
Antidepressants	006324	sertraline HCl
Antidepressants	001640	tranylcypromine sulfate
Antidepressants	001652	trazodone HCl
Antidepressants	001649	trimipramine maleate
Antidepressants	008847	venlafaxine HCl
Antidepressants	037597	vilazodone HCl
Antidepressants	040637	vortioxetine hydrobromide
Benzodiazepines	001617	alprazolam
Benzodiazepines	001656	amitriptyline/chlordiazepoxide
Benzodiazepines	001610	chlordiazepoxide HCl
Benzodiazepines	002037	chlordiazepoxide/clidinium Br
Benzodiazepines	001894	clonazepam
Benzodiazepines	001612	clorazepate dipotassium
Benzodiazepines	001615	diazepam
Benzodiazepines	004846	lorazepam
Benzodiazepines	001616	oxazepam
Other Stimulants	034868	armodafinil
Other Stimulants	010865	modafinil
Other Stimulants	045666	solriamfetol HCl
Sedatives	004480	diphenhydramine HCl
Sedatives	001650	doxepin HCl
Sedatives	004482	doxylamine succinate

Sedatives	006036	estazolam	Sedatives	040927	tasimelteon
Sedatives	026791	eszopiclone	Sedatives	001592	temazepam
Sedatives	001593	flurazepam HCl	Sedatives	001594	triazolam
Sedatives	001619	midazolam HCl	Sedatives	020347	zaleplon
Sedatives	033126	ramelteon	Sedatives	007842	zolpidem tartrate
Sedatives	041333	suvorexant			

Table 3. ICD-10 codes for relevant psychiatric diagnoses

ICD-10	Diagnosis
F20x	Schizophrenia
F31x	Bipolar Disorders
F32x-F33x	Major Depressive Disorder
F840	Autism
F91x	Conduct Disorders
F952	Tourette's disorder
F21x-F29x	Other Psychotic Disorders
F90x	ADHD
G474x	Narcolepsy
F5081	Binge Eating Disorder
G4733	Obstructive Sleep Apnea
F0281, F0391, F0151	Dementia with behavioral disturbance
R4585x, T1491	Homicidal and suicidal ideations; suicide attempt
F15x	Stimulant abuse

State Plan and "Excluded Drugs"

Excluded drugs a state **may opt to cover** (partial list):

- Agents when used for anorexia, weight loss or weight gain
- Agents when used for the symptomatic relief of cough and colds
- Prescription vitamins and mineral products (except prenatal vitamins and fluoride, which are not excluded)
- Nonprescription drugs (except tobacco cessation products must be covered in some circumstances)

State Plan and "Excluded Drugs"

CURRENT excluded drugs **Oregon opted to cover**:

- Agents when used for anorexia, weight loss or weight gain
  appetite stimulants for **anorexia, cachexia** and **wasting**
- Agents when used for the symptomatic relief of cough and colds
  cough preparations/expectorants, and cough & cold preps
- Prescription vitamins and mineral products
  vitamin K, folic acid preparations and vitamin D
- Nonprescription drugs
  1st gen. antihistamines & decongestant combos, diphenhydramine, antiulcer preps/gastrointestinal preps, non-narcotic analgesics

State Plan and "Excluded Drugs"

Excluded drugs a state **may NOT opt to cover** (partial list):

- Drugs when used for a cosmetic purpose or hair growth (unless the state determines medically necessary)
- Drugs when used for treatment of sexual or erectile dysfunction, and drugs solely FDA-approved for such uses

Imcivree™ (setmelanotide)[1,2]

Indications

- Chronic weight management in adult and pediatric patients 6 years and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants of POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.

Dosage

- If 12 years or older, inject 2 mg subcutaneously (SC) once daily for 2 weeks. If not tolerated decrease to 1 mg once daily. If 2 mg tolerated and additional weight loss desired increase to 3 mg.
- If 6 to less than 12 years, inject 1 mg SC once daily for 2 weeks. If initial dose not tolerated decrease to 0.5 mg daily. If 1 mg tolerated may increase by 1 mg increments to max dose of 3 mg daily.
- Supplied as 10 mg/mL, 1 mL multi-dose vial.

Background

- Functions as a melanocortin (MC) 4 receptor agonist with decreased MC3 and MC1 receptor activity. Central MC4 receptors affect regulation of hunger, satiety, and energy expenditure.
- POMC, PCSK1, and LEPR deficiency are associated with inadequate activation of MC4 receptor.
- Pharmacological treatments for obesity are not funded for adults or children. (Oregon Prioritized List Line 320, Guideline Note 5)[3]
- Medications for weight loss are excluded from OHA coverage. [Oregon Medicaid State Plan 12.a.1927(d)(2) and 12.a.1935(d)(2)][4]

Efficacy

Approval by the FDA was obtained with data from two identical, open-label, single-arm, 1-year trials. The trials included patients at least 6 years of age with a loss of function (LOF) variant for the POMC or PCSK1 genes (trial RM-493-012) or LEPR gene (trial RM-493-015) conferring a severe obesity phenotype. Those with recent intensive diet/exercise regimens or gastric bypass, psychiatric disorders including depression, and those with risk factors or dermatological findings concerning for melanoma (due to affinity for various melantocortin receptors) were excluded. After 12 weeks of therapy which included a 0.5 mg dose increase approximately every 2 weeks, patients continued with 10 weeks of open-label treatment. Patients who achieved at least 5 kg weight loss (or 5% if <100kg) entered a blinded withdrawal that involved 4 weeks of placebo then 4 weeks of active treatment. This was then followed by 32 weeks of open-label treatment. There were 21 total patients with at least 1 year of treatment, while 6 enrolled patients had not completed 1 year at the data cutoff and were excluded from the efficacy analysis. The patients were primarily adults > 16 years (62%), white (70-91%), female (50-73%), and with a median body mass index (BMI) of 40.0-46.6 kg/m^2. The primary endpoint was proportion of patients with >/= 10% weight loss from baseline at 1 year and the key secondary endpoint was the percentage change in bodyweight from baseline. The primary endpoint included the full analysis set (FAS), all patients who received study drug and at least one baseline assessment. The key secondary endpoint used the designated use set (DUS), all patients who received study drug and demonstrated at least 5 kg weight loss (or 5% if <100 kg) in the initial 12 week open-label period. However, the FDA also ran this analysis with the FAS population to reduce the selection bias of excluding patients who did not have an initial response.

	Study 1: POMC or PCSK1 (FAS N=10, DUS N=9)			Study 2: LEPR mutation (FAS N=11, DUS N=7)		
	Setmelanotide	P-Value	95% Confidence Interval	Setmelanotide	P-Value	95% Confidence Interval
Proportion with >/= 10% weight loss at 1 year from baseline (FAS)	8/10 (80%)	<0.0001	44.4% to 97.5%	5/11 (45.5%)	0.0002	16.8% to 76.6%
Percent weight change from baseline, Mean (SD) (FAS)	-23.1% (12.1%)	0.0003	-31.9% to -14.4%	-9.7% (8.8%)	0.0074	-16.0% to -3.3%

Safety

Common adverse reactions: injection site pain (96%), skin hyperpigmentation (78%), nausea (56%), headache (41%), diarrhea (37%), abdominal pain (33%), back pain (33%), fatigue (30%), vomiting (30%), depression (26%), upper respiratory tract infection (26%), spontaneous penile erection (23% males), arthralgia (19%), asthenia (19%), dizziness (15%), dry mouth (15%), dry skin (15%), insomnia (15%), vertigo (15%), and alopecia, chills, constipation, influenza-like illness, muscle spasm, pain in extremity, rash, suicidal ideation (11% for all).
Contraindications: none
Warnings and precautions: disturbance in sexual arousal (23% male, 7% female), depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi, risk of serious adverse reactions due to benzyl alcohol preservative in neonates and low birth weight infants
Special Populations: Not recommended in pregnant women unless benefit outweighs potential risks, avoid while breastfeeding, not recommended in moderate, severe, and end state renal disease.

Evidence Gaps/Limitations

- No studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions.

Recommendation

Designate drug as not covered per Oregon Medicaid State Plan.

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New Drug Evaluation: alglucosidase alfa, intravenous

Date of Review: April 2021
Generic Name: alglucosidase alfa

End Date of Literature Search: 12/31/2020
Brand Name (Manufacturer): Lumizyme™
Dossier Received: no

Research Questions:

1. What is the efficacy and effectiveness of alglucosidase alfa in reducing symptoms, improving functional outcomes, and improving mortality in patients with Pompe disease?
2. What are the harms of alglucosidase treatment in Pompe disease patients?
3. Are there subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from alglucosidase alfa?

Conclusions:

- There is insufficient evidence from one randomized, placebo-controlled trial in late-onset Pompe disease (LOPD) patients that treatment with alglucosidase alfa over 78 weeks resulted in a statistically significant improvement from baseline in the 6-minute walk test (6MWT) and percent predicted forced vital capacity (FVC) compared to placebo ([Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03) and (Mean difference 3.4% (95% CI, 1.0 to 5.8); p=0.006), respectively].[1-4] The clinical significance of a 28 m improvement in the 6MWT and a 3-point percentage change in % FVC in this patient population is unclear.
- There is low quality evidence from one small randomized open-label trial in patients with infantile-onset Pompe disease (IOPD) that treatment with alglucosidase alfa over 52 weeks resulted in increased proportion patients alive without need for ventilatory support (15/18 patients [83%]) compared to untreated historical controls (1/61 patients [2%]).[5,6] There were also 15/18 treated patients who showed reductions in left ventricular mass index (LVMI) [mean decrease 118 g/m^2 (range 45 to 193 g/m^2)], but the clinical significance of this change for individual patients with Pompe disease is unclear. [5,6]
- There is low quality evidence from one small non-randomized open-label trial that treatment with alglucosidase alfa over 2 years resulted in an increased proportion of patients alive at the end of treatment compared to historical controls [71% (95% CI, 52 to 91%) vs 26% (95% CI, 7 to 46%), respectively].[7]
- Alglucosidase alfa manufacturer label contains a black box warning about increased risk of anaphylaxis, hypersensitivity and immune-related reactions, as well as cardiorespiratory failure. Common adverse effects with alglucosidase alfa treatment ($\geq$ 5%) included rash, pyrexia, urticaria, flushing, and hypertension. [2]
- There is insufficient evidence regarding long-term safety and efficacy for the use of alglucosidase alfa in the treatment of Pompe disease. Evidence is limited by the small population of patients which have received alglucosidase alfa.

Recommendations:

- Add alglucosidase alfa to the PDL class for lysosomal storage disorders.

Author: David Engen, PharmD

- Designate alglucosidase alfa as non-preferred.
- Implement prior authorization (PA) criteria for alglucosidase alfa to ensure medically appropriate use.

Background:
Pompe disease, also known as glycogenosis type II or acid maltase deficiency, is an inherited, autosomal recessive lysosomal storage disease caused by mutations in the alpha-glucosidase gene which leads to a deficiency in the enzyme alpha glucosidase (GAA).[8,9] GAA mutations lead to a nonfunctional GAA enzyme and accumulation of glycogen stored in skeletal and cardiac muscle as well as other tissues.[8,9] Accumulation of glycogen due to GAA deficiency manifests in a wide disease spectrum from mild progressive myopathy without cardiac involvement to profound muscle weakness and hypotonia, respiratory distress, and hypertrophic cardiomyopathy.[8,9] Generally, early deficiencies in GAA activity result in rapid progression of disease and decline of motor function.[8,9] Although it is most common for Pompe disease to present within the first 2 months of life, it can also manifest at any age after infancy.[8,9] Early-onset Pompe disease with symptoms of cardiomyopathy, if left untreated, typically results in death from cardiorespiratory failure by the second year of life.[8,9]

Pompe disease prevalence differs greatly based on clinical variant, ethnic background and geography, and is estimated to affect roughly 1:40,000 people in the United States. In those with European descent, IOPD is rarer than LOPD with a prevalence of 1:100,000 compared to 1:60,000, respectively.[10] Pompe disease may affect African Americans at a rate as high as 1:14,000.[10] A study of Pompe disease in British Columbia, Canada revealed an incidence of 1 per 115,091 live births.[11] Some of the likely risk factors for development of Pompe disease include a family history of glycogen storage disease (Type 2) where at conception, siblings of a patient have a 25% chance of disease development.[10] A claims-based review from January through December 2020 revealed 14 patients in the Oregon Health Plan (OHP) population with a Pompe disease diagnosis, 3 of whom were Fee-for-Service (FFS) members. Since 2015, there have been 5 patients with FFS claims for alglucosidase alfa. Pompe disease is a funded condition on line 147 (glycogenosis) of the Health Evidence Review Commission (HERC) prioritized list of health services. Newborn screening (NBS) for Pompe disease is not currently mandatory in Oregon.

Pompe disease has been classified into two main phenotypes based on the age of onset, type of organs involved, progression rate, and severity.[12,13] Infantile-onset Pompe Disease (IOPD) often presents before 12 months of age (median age ~4 months), with rapid progression of symptoms such as muscle weakness, feeding issues, underdevelopment, and respiratory distress.[12] Most patients die within this stage without achievement of motor milestones such as turning over, sitting, or crawling.[12,13] Late-onset Pompe disease (LOPD) describes individuals who generally present after 12 months and without cardiac involvement.[12,13] The partial loss of GAA activity in LOPD results in less pronounced muscle dysfunction and slower overall decline compared to IOPD, although individuals may still eventually require a wheelchair and other assistive devices.[12,13] Respiratory dysfunction from intercostal and accessory muscle decline is common and may eventually lead to failure.[8,9] In LOPD, male gender and an earlier age of onset may predict a more rapid disease course.[12,13] There have been proposals to classify LOPD into a “childhood” form if symptom onset presents between birth and adolescence without progressive cardiac hypertrophy, and an “adult” form with symptom onset from adolescence into late adulthood.[12,13]

Table 1: General Characteristics of IOPD versus LOPD[12,13]

IOPD	LOPD
Onset <12 months old with cardiomyopathy	Onset <12 months **without** cardiomyopathy or Onset >12 months into adulthood
Typical age at diagnosis: <1-year-old	Typical age at diagnosis: roughly 40 years old
GAA enzyme activity <1% normal (Complete deficiency)	GAA enzyme activity 2%-40% of normal (Partial deficiency)
Rapid disease progression	Slow progression
Generalized muscle weakness	Proximal (core) muscle weakness
Respiratory distress	Respiratory insufficiency
Death <2 years old if untreated	Death 55 years (range 23-77 years) if untreated

The gene for GAA is located on chromosome 17 and hundreds of variations have been identified.[10,14] Although the majority of GAA gene mutations have proven to be pathogenic, there are also at least 67 nonpathogenic GAA mutations and 25 variations with an unknown effect.[10,14] Diagnosis of Pompe is accomplished by an acid alpha-glucosidase activity test obtained from dried blood spots and may be confirmed by a second test or by observance of 2 disease-causing GAA alleles via gene mutation analysis.[12,13] Less than 1% of normal GAA gene activity, or complete deficiency, is consistent with classic IOPD while partial deficiency (2%-40% of normal activity) is characteristic of non-classic IOPD and LOPD.[12,13]

There is evidence to suggest that the presence of cross-reactive immunological material (CRIM) may affect the prognosis of patients with IOPD.[15] By definition, GAA-deficient IOPD patients with at least some residual functional or non-functional enzyme are known as CRIM-positive patients while those with two GAA mutations and unable to synthesize the enzyme are called CRIM-negative.[15] Patients with late-onset Pompe disease are CRIM-positive because they have some residual GAA protein.[15] CRIM status is determined by Western blot analysis of patient fibroblast cells.[15] Research has shown that CRIM-positive patients tend to have a positive motor response to GAA gene-replacement therapies while CRIM-negative patients generally do not.[15] Along with clinical decline, high anti-rhGAA IgG antibody titers have been noted in many CRIM-negative patients whereas titers in CRIM-positive patients were low.[15] Patients who develop IgE antibodies to ERT may be at a higher risk for developing anaphylaxis and hypersensitivity reactions.[1,16,21] More research is needed to gain improved understanding of CRIM status as a predictive factor of clinical outcomes in Pompe disease.

Treatment for Pompe disease may include a variety of strategies which depend upon patient age, stage, genetic factors, and clinical manifestations.[12-14,17] Management usually requires a multidisciplinary approach with expertise in cardiology, pulmonology, metabolic disease, neurology, rehabilitation services, and nutrition support.[12-14] Respiratory, motor, and nutritional assessments are needed at regular intervals to track disease activity and monitor progress.[12-14] Some studies suggest that enhanced nutrition and exercise may help slow muscle function decline in LOPD patients.[12-14] A cardiology evaluation with echocardiography may be of value to monitor complications such as left ventricular mass index (LMVI) and risk of sudden cardiac death.[12-14,18] Respiratory surveillance is accomplished through regular chest X-rays and pulmonary function tests (PFTs) to ensure airway integrity.[12-14] For those patients with a need for respiratory support, supplemental oxygen or non-invasive ventilatory support may be warranted. Periodic assessment of musculoskeletal function via scoliosis tests and bone mineral density scans are also suggested.[12-14] Annual hearing evaluations and renal function studies, as well as periodic nutritional/feeding assessments are a crucial component in the effective management of patients with Pompe disease.[12-14] Enzyme replacement therapy (ERT) is typically started upon IOPD diagnosis or once symptomatic Pompe disease is recognized, although goals and expectations may differ between IOPD and LOPD.[12-14] The patient's

CRIM status is ascertained at the start of ERT therapy to assess the need for concomitant immune tolerance induction (ITI) therapy to optimize treatment and avoid the potential for immune-mediated reactions and poor outcomes. [2,12-14] ERT has been studied for many clinical outcomes in Pompe disease including mortality, respiratory function, ventilator dependence, and walking distance, but its effectiveness has shown mixed results.[19] Guidance for ERT initiation and discontinuation has been largely based on expert consensus, and some experts suggest discontinuing ERT if skeletal muscle function or respiratory function has not stabilized or improved within 2 years of treatment initiation.[20]

Table 2: Considerations for Starting and Stopping ERT[20]

Starting ERT	Stopping ERT
Confirmed Pompe disease diagnosis	Severe infusion-associated reactions that cannot be managed properly
Symptomatic disease	High antibody titers are detected that significantly counteract the effect of ERT
Patient commitment to regular treatment and monitoring	Patient wishes to stop ERT
Clinician commitment to regular treatment and monitoring	Patient does not comply with regular infusions or yearly clinical assessments
Residual skeletal and respiratory function on which to base assessments of functionally relevant and clinically important maintenance or improvement	No indication that skeletal muscle function and/or respiratory function have stabilized or improved in the first 2 years after start of treatment, based on clinical assessments
No co-morbid life-threatening illness in an advanced stage, where treatment to sustain life is inappropriate	Patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate

Clinically important outcomes for Pompe disease include morbidity, mortality, disease progression, ventilator use, and improvements in motor, pulmonary, or cardiac function. In clinical studies, the 6MWT has been used to measure gross motor function and the functional exercise level for daily physical activities in Pompe disease patients. Normal values for the 6MWT in healthy adults are at least 500 meters but can be as high as 700 meters in healthy adolescents.[1,21] The 6MWT has been extensively used to measure response to treatment in patients with chronic disease such as chronic obstructive pulmonary disease (COPD) and heart failure.[22] One study found the minimum clinical difference where patients noticed improvement was a mean change of roughly 40 meters from baseline, while patients noticed decline when the test was -70 meters worse than previous measurements.[22] For younger Pompe disease patients and notably in IOPD, the Alberta Infant Motor Scale (AIMS) has been employed to assess infant motor performance over time.[23] The AIMS is a standardized instrument that consists of 58 test items of 1 point each administered in 4 different positions with higher scores representative of more mature motor development.[23] The Peabody Developmental Motor Scale (PDMS-2) is a test of fine and gross motor abilities in areas such as reflexes, stationary, locomotion, object manipulation, grasping, and visual motor integration.[1,21] The PDMS-2 is used in children from birth through 83 months.[1,21] PDMS-2 raw scores are converted to a standardized 100 points where children with scores <80 are classified to be at risk. [1,21] The Pompe PEDI is used in children from roughly 6 months to 14 years old and measures mobility, function, and self-care in Pompe disease. [1,21] The Pompe PEDI is administered as a combination of interview questions and parent reported items scored as “capable” or “uncapable” then converted to a 0-100 continuum. [1,21] The higher the score, the more skills the child can perform. [1,21] The Short-Form Health Survey (SF-36) Physical Component score is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[24] The complete SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section and range from 0 - 100 where lower scores indicate more disability.[24] Pulmonary function assessment in Pompe disease patients is often obtained by measurement of forced vital capacity (FVC) and maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively).[21] Diaphragm weakness is suspected if there is a $\geq$10% decrease of FVC in the supine compared with the upright position; a $\geq$30% decrease indicates severe weakness.[25] In chronic diseases such as COPD, at least a 15% change over a year has been considered clinically meaningful.[25] Although the clinical relevance of the 6MWT, FVC, AIMS, PDMS-2, Pompe PEDI, and SF-36

have been utilized to assess progress for many chronic conditions, the significance of these outcomes and their respective minimal clinically important differences have generally not been validated in Pompe disease.[26]
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:
Alglucosidase alfa (Myozyme™, Lumizyme™) is a hydrolytic lysosomal glycogen-specific enzyme approved for use in patients with Pompe disease (acid alfa-glucosidase [GAA] deficiency).[1,2,21] Alglucosidase alfa is administered as an intravenous infusion at a dose of 20 mg/kg once every 2 weeks. [1,2,21] The FDA approved alglucosidase alfa under the name Myozyme™ in 2006 for the treatment of IOPD in infants and children up to 18 years old.[21] In 2010, FDA approved a second alglucosidase alfa product (Lumizyme™) to treat patients with late onset (non-infantile) Pompe disease at least 8 years of age or older without evidence of cardiac hypertrophy. [1,2,21] At the time, both GAA products were made from different processes and had not been analytically compared. A Risk Evaluation Mitigation Strategy (REMS) program was required for Lumizyme™ to ensure appropriate use according to age limitations and to monitor known risks of anaphylaxis and severe allergic reactions. [1,2,21] In 2014, the FDA reviewed a supplemental BLA for Lumizyme™ with manufacturer-supplied data from an immunogenicity study within the National Taiwan University Hospital (NTUH) newborn screening program.[1,2] The FDA found no evidence of a different antibody response in Lumizyme™ compared to Myozyme™.[1] Since the quality product critical attributes of both products were considered comparable, Lumizyme™ was granted expanded approval to treat all forms of Pompe disease based on safety and efficacy data of Myozyme™ and the REMS requirement was removed.[1,2] Currently, Lumizyme™ is the only formulation available for use in the United States.

Alglucosidase alfa (Lumizyme™) in the treatment of Pompe disease was assessed in one pivotal randomized, double-blind placebo-controlled trial in LOPD patients and in two open-label, historically controlled, multicenter clinical trials in IOPD patients (**Table 5**).

The Late Onset Treatment Study (LOTS) assessed the safety and efficacy of alglucosidase alfa in a randomized, placebo-controlled, 78-week trial in 90 LOPD patients.[1-3] Patients were randomly allocated in a 2:1 ratio to either alglucosidase alfa 20 mg/kg (n=60) or placebo (n=30).[1,3] Baseline characteristics were generally similar, however the alglucosidase alfa group had slightly more men, were older, and generally required less walking device assistance.[1,3] In addition, age of disease symptom onset was different between groups for the alglucosidase alfa versus placebo groups (30 vs. 24 years old, respectively).[1,3] Patients were generally ambulatory; however, almost half required a walking device, and roughly one-third required some type of ventilator support. [1,3] Mean age at first infusion was roughly 43 years old although ages ranged between 10 and 70 years old. [1,3] Patients were excluded if they required invasive ventilator support (as defined by use of an endotracheal tube), or requirements for noninvasive ventilatory support while awake and in an upright position. [1,3] The primary outcomes were distance walked in the 6-minute walk test and percentage of predicted forced vital capacity (FVC). [1,3] Relevant clinical secondary outcomes included percent of predicted quantitative muscle strength testing, percent of predicted maximum inspiratory and expiratory pressure, and Short-Form Health Survey (SF-36) Physical Component score change from baseline. [1,3]

There were 81 of 90 patients who completed the trial. [1,3] At 78 weeks, a statistically significant difference from the baseline 6MWT was observed in the alglucosidase alfa group compared to placebo (+25.1 m vs. -3.0 m, respectively; Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03). [1,3] There was also a statistically significant change observed from baseline in percent predicted FVC compared to placebo (+1.2 versus -2.2, respectively; Mean difference 3.4% [95% CI, 1.0 to 5.8]; p=0.006). [1,3] No statistically significant changes were observed in the clinically relevant secondary outcomes except for percent predicted maximum expiratory pressure, which reported a slight increase in favor of alglucosidase alfa versus placebo (mean difference 3.8 [95% CI, 0.3 to 7.3]; p=0.04).[1,3]

There was no statistically significant difference in quantitative muscle testing, maximum inspiratory pressure, or SF-36 Physical Component scores. [1,3] A follow-up LOTS extension study lasted 26 additional weeks and yielded similar results for alglucosidase-treated individuals. [1,4] However, when patients in the placebo arm of LOTS were switched to alglucosidase alfa in LOTS Extension, the 6MWT and FVC showed no further deterioration but did not show improvement after 6 months of active treatment. [1,4]

In an open label, phase 2/3 study by Kishnani et. al (AGLU01602), alglucosidase alfa efficacy was assessed in 18 patients (11 males, 7 females) aged 6 months or less (mean 4.6 months) for the treatment of infantile-onset Pompe disease.[1,5,21] Patients were randomized 1:1 and given alglucosidase alfa at either a 20 mg/kg or 40 mg/kg IV infusion once every 2 weeks for 52 weeks. [1,5,21] Doses were adjusted every 4 weeks if needed to account for body weight changes. [1,5,21] The primary endpoint was the proportion of patients alive with no need for invasive ventilation support at 18 months of age compared to survival rates of the age-matched historical control group. [1,5,21] Invasive ventilator-free survival was defined as 1) patient was ventilator free for a 14-day period encompassing the target time point or 2) if the investigator determined that ventilator use was due to a secondary cause at the target time and then the patient was to be followed for 30 more days.[21] If during the follow up period the patient became ventilator-free for 14 consecutive days, the patient was considered ventilator-free.[21] Invasive ventilation was defined as requiring passive ventilation through an endotracheal tube or tracheostomy. [1,5,21] At 52 weeks, 15/18 (83%) patients treated with alglucosidase alfa were alive without need for ventilatory support at 18 months compared to 1 of 65 patients (2%) in the historical cohort. [1,5,21] Although the investigators reported no significant difference between the low-dose and high-dose groups, no data was reported for comparison between doses. For secondary outcomes, there were notable improvements in LVMI [mean decrease 118 g/m^2 (range 45 to 193 g/m^2; n=15)] and 13/18 (83%) of patients demonstrated motor improvements on the AIMS and/or Pompe PEDI score compared to baseline. [1,5,21] With treatment beyond 52 weeks, it was noted, however, that 4 patients required ventilator support and 2 of them died, 1 at 14 months and the other at 25 months.[1,5,21] The extension phase of the study (AGLU02403) was up to 3 years which included 16 surviving patients from the original 18.[1,6,21] The study was identical to AGLU01602 but without randomization. [1,6,21] Of the 16 enrolled patients, 13 completed the study, 2 patients died while in study participation, 1 patient withdrew from the study then died after withdrawal, while one additional patient died after study completion. [1,6,21]

In an open-label, non-randomized study by Nicolino et. al (AGLU01702), the efficacy and safety of alglucosidase alfa was examined in 21 patients with IOPD.[1,7,21] Patients received alglucosidase alfa 20 mg/kg every other week or an escalated dose of 40 mg/kg for up to 168 weeks (median 120 weeks).[1,7,21] The trial included 18 CRIM-positive and 3 CRIM-negative patients between the ages of 3 to 3.5 months at the time of first infusion. [1,7,21] There were 5 patients on invasive ventilatory support at the first infusion. [1,7,21] The primary outcome was the proportion of patients alive at the end of treatment. [1,7,21] Only the results of the primary analysis were compared to an untreated reference cohort of 168 IOPD patient cases. [1,7,21] At the end of 52 weeks, the proportion of patients alive at the end of treatment was higher in the alglucosidase alfa-treated group compared to historical control reference group [71% (95% CI, 52 to 91%) vs 26% (95% CI, 7 to 46%), respectively].[7,21] Of the 16 patients free of invasive ventilatory support at baseline, 44% (7/16) remained free of invasive ventilation, 4 had become ventilator dependent, and 5 patients had died. [1,7,21] These outcomes were not compared to the untreated reference cohort.[1,7,21] A Kaplan Meier method was used to calculate survival estimates at both 52 weeks and 104 weeks for treated patients compared to the untreated historical reference cohort. [1,7,21] Select secondary outcomes of functional assessments were inconsistently reported and could not be compared to historical control due to limited availability of detailed data regarding clinical outcomes. [1,7,21]

It is unclear whether a 28-meter improvement in the 6MWT and a 3-point percentage change in the % FVC after 78 weeks of alglucosidase alfa treatment is a clinically meaningful difference in Pompe disease patients. Since the 6MWT allows patients to rest when desired, it may not be the optimal measurement of maximum exercise capacity in treatment outcomes for Pompe Disease. In the LOTS study, patients in the alglucosidase alfa group were older than the placebo group, and the placebo group also had more walking device use. Given the progressive nature of Pompe disease, this may indicate groups were not comparable

and could have biased results in favor of treatment. For measures of cardiac function, there are no correlations between changes in LVMI and clinical improvements in meaningful outcomes for patients treated with alglucosidase alfa compared to historical controls. Although many patients were reported to have clinically meaningful gains in motor development per the AIMS and Pompe PEDI assessments with alglucosidase alfa treatment, the FDA noted that these patients remained significantly delayed compared to normal age-matched peers, so longer-term follow-up is needed.[1,21] The relatively small number of patients studied in these trials present many challenges to interpretation of the data. In the IOPD studies, only 7 of the 39 patients were CRIM negative so efficacy in this population is unclear. Differences in time from diagnosis, disease severity, and patient ages were not described in detail for all trials which made it difficult to determine what patient populations might respond better (or worse) to ERT. In addition, without details of the patient selection process it is unclear if a historical control group would be an accurate or appropriate comparator. It was unknown if historical controls were appropriately matched based on major prognostic factors such as baseline respiratory and motor function. There may have been changes in standards of care over time such as more access to ventilation access to mobility assistive devices, physical therapy among other important advances among the historical control population. There were no standardized tools used in the trials to measure patient quality of life (QOL), and the available data indicates little to no improvement in QOL, so outcomes in these areas remain mostly unknown. For many of the trials, raw measurements were not reported and there was no comparator group, so assessment of the benefit magnitude and effectiveness of therapy were not possible. More trials with larger numbers of patients are needed to evaluate whether treatment with alglucosidase alfa provides long-term survival benefit, sustained stabilization or improvement of muscle, motor and/or respiratory function, or quality of life improvements in Pompe disease patients.

Clinical Safety:

Safety for the use of alglucosidase alfa in the treatment of IOPD patients is based on over 3 years of clinical trial data in 39 patients.[1,2] Most adverse events occurred either during or within 2 hours of administration. [1,2] Common infusion reactions included rash, pyrexia, urticaria, flushing, and hypertension. In studies with LOPD patients (N=90) treated with alglucosidase alfa, adverse effects were reported compared to placebo. [1,2] Common adverse reactions in at least 5% of alglucosidase-treated patients and at a greater frequency than placebo-treated patients are listed in **Table 3**. [1,2] Hyperhidrosis, fatigue, myalgia, and nausea were reported by patients within 2-48 hours after completion of the alglucosidase alfa infusion. [1,2]

Table 3 Adverse Events in at least 5% of Patients treated with Alglucosidase Alfa in Clinical Trials[1,2]

IOPD Patients	(n=39)		**LOPD Patients**	Alglucosidase alfa (n=60)	Placebo (n=30)
Adverse Events	**N (%)**		**Adverse Events**	**N (%)**	**N (%)**
Rash	7 (18)		Hyperhidrosis	5 (8)	0 (0)
Pyrexia	6 (15)		Urticaria*	5 (8)	0 (0)
Urticaria*	5 (13)		Anaphylaxis	4 (7)	0 (0)
Flushing*	5 (13)		Chest discomfort	4 (7)	1 (3)
Increased blood pressure*	4 (10)		Muscle twitching	4 (7)	1 (3)
Decreased Oxygen Saturation	3 (8)		Myalgia	3 (5)	1 (3)
Cough	3 (8)		Flushing*	3 (5)	0 (0)
Tachypnea	3 (8)		Increased blood pressure*	3 (5)	0 (0)
Tachycardia	3 (8)				
Erythema	2 (5)				

Vomiting	2 (5)				
Rigors	2 (5)				
Pallor	2 (5)				
Cyanosis	2 (5)				
Agitation	2 (5)				
Tremor	2 (5)				

(* = Common adverse events reported in both trials)

FDA labeling has a black boxed warning (BBW) for the possibility of life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions with alglucosidase alfa infusions. [1,2] Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. [1,2] Prescribers should provide close patient observation during and after alglucosidase alfa administration and be prepared for appropriate medical management of hypersensitivity and anaphylaxis. [1,2] The majority of patients developed IgG antibodies to alglucosidase alfa within 3 months of treatment. [1,2] Evidence from studies suggest that patients with high and prolonged IgG antibody titers may experience reduced clinical response such as loss of motor function, ventilator dependence, or possibly death. [1,2] The manufacture has suggested patients be monitored for IgG antibody formation every 3 months for 2 years and then annually.[1,2] There is also a BBW for IOPD patients with compromised cardiac or respiratory function in that they may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload and require additional monitoring.[1,2]

Look-alike / Sound-alike Error Risk Potential: Lumizyme™ may be confused with Lumigan™ (bimatoprost) or Lumason™ (Sulfur Hexafluoride Lipid-Type A Microspheres)

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Survival
2) Functional or symptom improvement
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) 6MWT
2) FVC
3) Survival
4) Invasive ventilator support

Table 4. Pharmacology and Pharmacokinetic Properties. [1,2]

Parameter	
Mechanism of Action	Recombinant, exogenous source of acid alpha-glucosidase (GAA) that binds to lysosomes and is internalized, resulting in increased enzymatic activity in cleaving glycogen
Oral Bioavailability	N/A – administered intravenously
Distribution and Protein Binding	Vd: Infants 1 to 7 months: 96 ± 16 mL/kg
Elimination	N/A
Half-Life	2.3 hours (infants 1-7 months); 2.4 hours (adults)
Metabolism	Unknown – not studied

Abbreviations: hr = hours; kg = kilogram; L = liters; Vd = volume of distribution

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. van der Ploeg T, et al.[1,3] Phase 3 MC, DB, PC N=90	1. alglucosidase alfa 20 mg/kg IV every 2 weeks x 78 weeks (n=60) 2. Placebo IV every 2 weeks x 78 weeks (n=30)	Demographics: -Mean age: 45 years (range 16-70 years) -Male/Female: 1. 57%/43% 2. 37%/63% -Race: White (93%) -Mean disease duration: 9.5 years -Baseline 6MWT 1. 332.2 m 2. 317.9 m -Baseline mean % predicted FVC 1. 55.4% 2. 53.0% -Use of walking device 1. 38% 2. 53% -Use of ventilatory support 1. 33% 2. 37% Key Inclusion Criteria: -confirmed Pompe's disease Dx (GAA deficiency and 2 GAA gene mutations) -≥8 years or older -able to walk 40 m on 6MWT (assistive devices permitted) -% predicted FVC 30% - 80% in upright position, with postural drop in FVC (in L) of ≥10% -muscle weakness in lower extremities (bilateral knee extension > 80% predicted per QMT Key Exclusion Criteria: -any invasive ventilation -noninvasive ventilation while awake and upright -any previous GAA enzyme replacement -major condition that interfered with study compliance or monitoring	ITT: 1. 60 2. 30 Attrition: 1. 5 (8.3%) 2. 4 (13.3%)	Primary Endpoint: 6MWT distance change from baseline 1: +25 m 2: -3 m Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03) Percent predicted FVC in the upright position 1. 1.2% 2. -2.2% Mean difference 3.4% (95% CI, 1.3 to 5.5) p-value = 0.006 Secondary Endpoint: % predicted maximum expiratory pressure 1. 3.2 2. -0.6 Mean difference 3.8 (95% CI, 0.2 to 7.3) P=0.04	NA for all	Outcome: TEAEs 1. 32 (53.3%) 2. 17 (56.7%) SAEs 1. 13 (22%) 2. 6 (20%) Most common AEs -hyperhidrosis 8% -urticaria 8% -anaphylaxis 7% -chest discomfort 7% -muscle twitching 7% Statistical significance not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) IVRS with central computer used but details of randomization and allocation concealment not described; older age of disease onset in treatment group and imbalances in use of walking devices may indicate placebo group has more progressive or severe disease; more males in treatment group Performance Bias: (Unclear) Investigators, patients blinded; Unknown if patient care received was standardized; Manufacturer's Clinical Pharmacy Research Services not blinded Detection Bias: (High) Blinding of outcome assessors not described; independent statistical center and the Data Safety Monitoring Board were unblinded to treatment assignment during interim analysis and review Attrition Bias: (Low) Overall attrition low; sensitivity analysis performed; LOCF and regression model approach was used to create multiple imputations for missing data; worst rank analysis also used Reporting Bias: (Low) All results reported Other Bias: (High) Manufacturer funded the study and its employees involved in preparation and review of the paper **Applicability**: Patient: All LOPD patients; ambulatory; naive to ERT; patients with major condition that interfered with study compliance or monitoring were excluded; lack of ethnic minority inclusion as Pompe may be more common in African American patients Intervention: Alglucosidase alfa 20 mg/kg IV biweekly Comparator: Placebo Outcomes: Primary outcome (% predicted FVC) is a surrogate endpoint; long-term impact on survival, muscle, motor, and respiratory development unknown. Setting: Multinational (Netherlands, France, U.S.)

2. Kishnani PS, et al.[1,5,21] Phase 2/3 (Plus 52-week follow up extension study) MC, OL, randomized N=18	1. alglucosidase alfa 20 mg/kg every 2 weeks x 52 weeks 2. alglucosidase alfa 40 mg/kg every 2 weeks X 52 weeks Untreated historical control (N=61)	Demographics: -Gender: Male 61% -Race: White 39% Black 22% Asian 17% Hispanic 11% -Mean age at first symptoms: 1.6 mo. -Mean age at diagnosis: 3.7 mo. -Mean age at first infusion: 4.6 mo. Key Inclusion Criteria: - documented symptoms of IOPD - skin fibroblast GAA activity <1% of normal mean -hypertrophic cardiomyopathy (LVMI 65g/m^2 by echocardiogram) - age <26 weeks at enrollment Key Exclusion Criteria: -Respiratory insufficiency (O_2 saturation ≤90% or CO_2 partial pressure 55 mmHg (venous) or 40 mmHg (arterial) in room air or any ventilator use -Major congenital anomaly or clinically significant intercurrent illness unrelated to Pompe disease -Any prior alglucosidase alfa treatment	ITT: 1. 9 2. 9 Attrition: 1. 1 2. 0	Primary Endpoint: Survival without ventilatory support at 52 weeks -Treated combined: 15/18 (83%) -Untreated historical control: 1/61 (2%) Secondary Endpoints: Motor Development improvements in AIMS and/or Pompe PEDI: 13/18 (72%) (no scoring details reported) Cardiomyopathy, Change in LVMI: -mean decrease 118 g/m^2 (range 45 to 193 g/m^2) N=15	NA for all	Outcome: Development Anti-rhGAA IgG antibodies -16/18 (89%) Severe AEs -15/18 (83%) IARs -11/18 (61%) Discontinuations due to IARs or AEs -none Deaths 2/18 (11%) -during follow-up period Statistical significance not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) No details of randomization strategy or allocation concealment; open-label potential exclusion of sickest patients (e.g., severely respiratory compromised) could overestimate survival of treatment group. Historical control group selected based on age at first symptoms, age at diagnosis, and other screening criteria for the clinical trial (process not detailed). Treatment and historical controls with similar demographic profiles. Performance Bias: (High) No blinding of clinicians or participants. Timing of infusion was unknown. Detection Bias: (Low) Outcome assessments of echocardiogram and muscle biopsies centrally reviewed by blinded pediatric cardiologist and pathologist. Centralized scoring of motor and cognitive evaluations by non-blinded clinician Attrition Bias: (Low) 1 death in 20 mg/kg group before 52 weeks Reporting Bias: (Unclear) Blood chemistry safety data not reported. No data regarding outcome comparisons between different treatment doses. All other outcomes reported. Other Bias: (High) Primary authors received grant support from Genzyme and were members of disease advisory board for Genzyme. **Applicability**: Patient: IOPD patients age <26 weeks at enrollment Intervention: alglucosidase alfa 20 mg/kg/2 weeks and 40 mg/kg/2 weeks Comparator: Historical control Outcomes: Survival and ventilator use Setting: Multinational USA – 6 centers Europe – 5 centers Taiwan – 1 center Israel – 1 center

3. Nicolino et al. [1,7,21] Phase1/ Phase2 Single arm, OL, Non-randomized N=21	alglucosidase alfa 20 mg/kg IV up to 40 mg/kg every 2 weeks x 52 weeks plus 52-week follow-up Untreated historical control group (N=168)	Demographics: Age range: 3-43 months (median 13 months) Male: 48% Race -White: 71% -Asian: 14% -Black: 10% Median Age at first symptoms: 3 months Median Age at diagnosis: 6.8 months Invasive ventilator support at baseline: 5 (24%) Noninvasive ventilator support (baseline): 2 (10%) LVMI: 193.8 g/m^2 Key Inclusion Criteria: - Pompe disease symptoms by 12 months of age -Skin fibroblast GAA activity ≤2% of normal mean -Age 6–36 months at enrollment -Abnormal left ventricular mass indices (LVMIs) defined as ≥65 g/m^2 for patients up to 12 months old or >79 g/m^2 for patients older than 12 months Key Exclusion Criteria: -Clinical signs or symptoms of cardiac failure with ejection fraction <40% -Major congenital anomaly -Intercurrent organic disease (metabolic disorders) -Prior treatment with ERT	ITT: 21 Attrition: 0	Primary Endpoint: 2-year survival estimate: -Treatment: 71% (95%CI, 52 to 91) -Untreated historical Control : 26% (95% CI, 7 to 46) Secondary Endpoints Unable to compare treated patient outcomes to historical reference cohort. Raw data were not available. Should not be used to establish efficacy. Respiratory function: -Free of ventilator dependency: 44%	NA for all	Outcome: Antibody development 19/20 (95%) SAEs 18/21 (86%) -pneumonia: 8(38%) -respiratory distress: 6 (29%) -respiratory failure 5 (24%) Most common IARs -subcutaneous skin disorders 13/21 (62%) -vascular disorders 10/21 (48%) -blood pressure increases 7/21 (33%) Heart/respiratory rate increases 7/21 (33%) Death 6/21 (29%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Non-randomized; broader study population than inclusion criteria stated (older, younger) Performance Bias: (High) Open label study design with no blinding of most study personnel Detection Bias: (Unclear) LVH assessment was confirmed by a central, blinded cardiologist but no details; interim analysis performed at 26 weeks Attrition Bias: (Low) No withdrawals reported Reporting Bias: (Unclear) KM analysis may have overestimated benefit; no rationale for censored patients described; actual values for some secondary outcomes not reported Other Bias: (High) Funded by manufacturer. Primary authors received editorial assistance from Genzyme. **Applicability**: Patient: Patients with IOPD Intervention: alglucosidase alfa 20 mg/kg IV up to 40 mg/kg IV Comparator: None (historical) Limits conclusions regarding efficacy of treatment or long-term safety. Functional outcomes also compared to historical control. No patient to patient matching occurred for historical control and important markers of disease progression were not reported including pulmonary function details and non-pharmacological therapy (e.g., assistive devices, ventilator support, etc). Outcomes: Survival Setting: Multinational (US, France, Israel, UK)

Abbreviations: AIMS = Alberta Infant Motor Scale; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double blinded; Dx = diagnosis; ERT = enzyme replacement therapy; FVC = forced vital capacity; GAA = enzyme alpha glucosidase; IARs = Infusion Associated Reactions; IOPD = infantile onset Pompe disease; ITT = intention to treat; IV = intravenous; IVRS = interactive voice response system KM = Kaplan-Meier; L = liters; LOCF = last observation carried forward; LOPD = Late onset; PC = placebo controlled; Pompe disease; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MC = multicenter; mITT = modified intention to treat; M = meter; Mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PDMS-2 = Peabody Developmental Motor Scale; PP = per protocol; QMT = quantitative muscle testing; SAEs = serious adverse events; TEAEs = treatment emergent adverse events; UK = United Kingdom; US = United States; 6MWT= six minute walk test

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUMIZYME® (alglucosidase alfa), for injection, for intravenous use

Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

- **Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur. (5.1, 5.2)**
- **Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring. (5.3)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2, 5.5, 5.6) 02/2020

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

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency). (1)

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

- 20 mg per kg body weight administered every 2 weeks as an intravenous infusion. (2)

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

- For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-use vial for reconstitution. (3)

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

None. (4)

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

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment. (5.1)
- Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs. (5.2)
- Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion. (5.3)
- Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion. (5.4)
- Risk of Antibody Development: Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. (5.5)

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

The most frequently reported adverse reactions (≥5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia (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: 02/2020

Alglucosidase alfa

Goal(s):

- Ensure medically appropriate use of alglucosidase alfa for the treatment of Pompe disease

Length of Authorization:

Up to 12 months

Requires PA:

- Alglucosidase alfa (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/

Table 1: FDA-approved Dosage and Administration

Indication	Dosing Regimen
Pompe Disease	20 mg/kg IV once every 2 weeks

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the treatment for the diagnosis of Pompe disease confirmed by either DNA testing or enzyme assay (e.g. acid alpha-glucosidase activity test)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the agent dosed appropriately based on documentation of patient weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #7. Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the request for treatment of infantile-onset Pompe disease (IOPD)?	**Yes:** Go to #8	**No:** Go to #11
8. Has the provider documented a baseline value for ALL the following assessments? • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status? • Cardiac imaging (e.g. chest x-ray, echocardiography)? • CRIM status?	**Yes:** Document baseline results and go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient CRIM-negative?	**Yes:** Go to #10	**No:** Approve for 3 months If approved, a referral will be made to case management by the Oregon Health Authority.
10. Is there documentation that concomitant immune tolerance induction (ITI) therapy will be initiated with enzyme replacement therapy (ERT)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient at least 5 years of age or older?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is there a baseline documentation for both of the following? • Pulmonary function test (PFT) with spirometry including baseline percent predicted forced vital capacity (FVC) value 30 to 79% of predicted value while in the sitting position • Demonstration of completed 6-minute walk test (6MWT) of at least 40 meters with or without an assistive device -OR- Muscle weakness in the lower extremities?	**Yes:** Approve for 6 months Document baseline results. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the provider documented a baseline value for both the following assessments: • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status?	**Yes:** Approve for 3 months Document baseline results. 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 there documented evidence of adherence and tolerance to the approved infusion therapy regimen through claims history and/or provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh, Deny; medical appropriateness
2. Is this the first renewal of alglucosidase alfa therapy?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Is there documentation that the patient has recently been tested* for IgG antibody formation? * = *Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.*	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the agent dosed appropriately based on documentation of patient weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #6 Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Is patient under 5 years old?	**Yes:** Approve for 3 months	**No:** Go to #7
7. Has the patient received alglucosidase alfa for at least 6 months?	**Yes:** Approve for 12 months	**No:** Approve for 3 months

P&T/DUR Review: 4/21 (DE)
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 Review with New Drug Evaluation: Biologics for Autoimmune Disorders-Neuromyelitis Optica Spectrum Disorder

Date of Review: April 2021

Date of Last Review: n/a
Dates of Literature Search: 1/1/1996 – 1/20/2021
Brand Name (Manufacturer):
Soliris® (Alexion Pharmaceuticals)
Uplizna™ (Viela Bio)
Enspryng™ (Genentech/Roche)
Dossiers Received: Yes

Generic Name:
Eculizumab
Inebilizumab-cdon
Satralizumab-mwge

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

Purpose for Class Update:
To define place in therapy for 3 immunosuppressive agents, eculizumab, inebilizumab-cdon, and satralizumab-mwge, recently approved by the Food and Drug Administration (FDA) for the treatment adults with neuromyelitis optica spectrum disorder (NMOSD).

Research Questions:
1. What is the effectiveness of eculizumab, inebilizumab, and satralizumab in reducing time to relapse in adult patients with NMOSD who are anti-aquaporin-4 (AQP4) antibody positive?
2. What are the harms of eculizumab, inebilizumab-cdon and satralizumab in adults with NMOSD?
3. Is there comparative evidence that eculizumab, inebilizumab, and satralizumab differ in efficacy or harms for management of NMOSD?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which eculizumab, inebilizumab, or satralizumab may be beneficial or cause more harm?

Conclusions:
Eculizumab
- A phase 3, double-blind, time-to-event, multicenter trial evaluated the safety and efficacy of eculizumab in adults (n=143) with highly active AQP4-IgG seropositive NMOSD.[1] In the PREVENT trial, eculizumab was primarily add-on therapy, 78% of patients at baseline were receiving a stable-dose regimen of immunosuppressive therapy (IST) including chronic corticosteroids.[1] The primary end point was the number of adjudicated initial relapses compared to placebo.[1] Moderate quality evidence shows adjudicated relapses occurred in 3% of subjects in the eculizumab group and 43% of subjects in the placebo group (hazard ratio [HR], 0.06; 95% confidence interval [CI], 0.02 to 0.20; P<0.001; Number Needed to Treat [NNT] 3) over the follow-up period (median

follow-up period: 90 weeks for active drug and 43 weeks for placebo).[1] A significant reduction in adjudicated annualized relapse rate was observed in patients treated with eculizumab compared with placebo (0.02 in the eculizumab group vs. 0.35 in the placebo group rate ratio [RR], 0.045; 95% CI, 0.013 to 0.151; P<0.0001).[1] The mean change in the Expanded Disability Scale Score (EDSS) score (range 0 to 10) from baseline was not significantly different between the 2 treatment arms (-0.18 in the eculizumab group and 0.12 in the placebo group; least-squares mean difference [LSMD], –0.29; 95% CI, –0.59 to 0.01).[1] The median change in EDSS was 0 for both treatment groups, and over 70% of eculizumab-treated patients had the same or experienced worsening of their EDSS scores at the end of study assessment.[2]

- Eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections which was identified in initial trials evaluating eculizumab use in indications other than NMOSD.[3] Healthcare providers who prescribe eculizumab must enroll in the Solaris® Risk Evaluation and Mitigation Strategy (REMS) restricted program.[3]
- In the PREVENT trial, upper respiratory tract infections (29% vs. 13%), nasopharyngitis (21% vs. 19%), back pain (16% vs. 15%), and dizziness (15% vs. 13%) were more common in the eculizumab group compared with the placebo group.[1]

Inebilizumab

- N-MOmentum was a phase 2/3 double-blind trial that evaluated the safety and efficacy of inebilizumab as monotherapy in reducing the risk of relapse and disability in adults with AQP4 seropositive or seronegative NMOSD. Ninety-three percent (n=213) of enrolled subjects were AQP4 seropositive.[4] The primary endpoint was to compare the efficacy of inebilizumab with placebo in reducing the risk of NMOSD attack in patients.[4] Moderate-quality evidence showed 12% of 174 participants receiving inebilizumab in the intention-to-treat (ITT) population had an attack versus 39% of 56 participants receiving placebo (hazard ratio (HR) 0.272; 95% CI 0.150 to 0.496; p<0.0001; NNT 4) before day 197 of the trial.[4] In the AQP4 seropositive population, 11% of patients receiving inebilizumab had an attack compared with 42% of patients receiving placebo treatment (HR 0.227; 95% CI 0.121 to 0.423; p<0.0001; NNT 4).[4] Among the 17 AQP4-seronegative patients who were randomly allocated to treatment (13 to inebilizumab), three attacks occurred, all in the inebilizumab group.[4] Because only four AQP4-seronegative patients were randomly allocated to placebo and no attack occurred in this group, inebilizumab efficacy could not be interpreted in the AQP4-seronegative cohort.[4]
- Across both the randomized and open-label treatment in the N-MOmentum trial, the most common adverse reactions (greater than or equal to 10%) were urinary tract infection (20%), nasopharyngitis (13%), infusion reaction (12%), arthralgia (11%), and headache (10%).[5] Inebilizumab can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, or rash.[5] During the randomized clinical trial period, infusion reactions were observed with the first course of inebilizumab in 9% of AQP4 seropositive NMOSD patients and 10% of patients in the placebo arm.[5] Premedication with IV methylprednisolone 80 mg to 125 mg, oral diphenhydramine 25 mg to 50 mg and oral acetaminophen 500 mg to 650 mg is recommended prior to each infusion to reduce the frequency and severity of infusion reactions.[5]

Satralizumab

- The safety and efficacy of satralizumab in NMOSD patients were evaluated in two phase 3, randomized, placebo-controlled, multicenter, double-blinded studies with open-label extensions.[6,7] In both studies, the primary endpoint was evaluated in the ITT population, consisting of both AQP4 seropositive and AQP4 seronegative patients, and measured the time to first protocol-defined relapse (PDR).[6,7] SAkuraSky[6] investigated satralizumab added to baseline IST in adolescents and adults (n=83), while SakuraSTar[7] evaluated satralizumab monotherapy in adults (n=95). Enrollment of AQP4 seronegative patients was limited to 30% in both trials to reflect estimated prevalence in the NMOSD population.
- Moderate-quality evidence from the SAkuraSky trial showed that among patients who received satralizumab, 20% (n=8) experienced a PDR compared with 43% (n=18) of patients who received placebo (HR 0.38; 95% CI, 0.16 to 0.88; p=0.02; NNT 5).[6] In AQP4-IgG seropositive patients, 11% of satralizumab-treated

patients experienced a PDR at week 48 compared with 43% of placebo-treated patients (HR=0.66; 95% CI: 0.06-0.75; p=0.0086; moderate quality evidence).[6] Two key quality of life (QoL) secondary end points were the change from baseline to week 24 in the visual-analogue scale (VAS) pain score (range, 0 to 100, with higher scores indicating more pain) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (range, 0 to 52, with lower scores indicating more fatigue). There were no significant differences in pain or fatigue reported between treatment groups.[6]

- In the SakuraSTar trial, moderate quality evidence showed that relapses occurred in 19 (30%) patients receiving satralizumab and 16 (50%) receiving placebo (HR 0.45, 95% CI, 0.23 to 0.89; p=0.018, NNT 5).[7] In AQP4-IgG seropositive patients, satralizumab showed a 74% reduction in the risk of relapse (HR=0.26; 95% CI: 0.11 to 0.63; moderate quality evidence).[7] The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.[7]
- The most common risks of treatment with satralizumab were an increased risk of several types of infections (nasopharyngitis, upper respiratory tract infection), headache, rash, arthralgia, extremity pain, fatigue, and nausea. Other IL-6 antagonists (sarilumab and tocilizumab) have boxed warnings for serious infections and potential tuberculosis or hepatitis B reactivation.[8]

Biologics for NMOSD

- No head-to-head trials have provided comparative evidence that eculizumab, inebilizumab, and satralizumab may differ in efficacy or harms for management of NMOSD. There is insufficient comparative evidence to evaluate functional status, quality of life, and disability.
- There is insufficient evidence to demonstrate specific sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) may have more benefit or reduced harm with eculizumab, inebilizumab, or satralizumab.

Recommendations:

- Create a new class of drugs on the PDL entitled “Biologics for Rare Diseases” and include eculizumab, inebilizumab, satralizumab in this new class.
- Implement clinical prior authorization (PA) criteria for each biologic agent to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (**Appendix 4**).
- Review costs in Executive Session.

Background:

NMOSD or Devic’s disease, is a rare, autoimmune, severe demyelinating disease of the central nervous system that predominantly involves inflammation of the optic nerve and spinal cord.[9] The pathogenesis is unknown, but it appears to be related to B-cell autoimmunity directed against aquaporin-4, the dominant water channel in the central nervous system. Features of NMOSD include acute attacks of rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course.[9] Neuromyelitis optica had long been considered a subtype of multiple sclerosis (MS) due to the similarities between the clinical presentations of MS and NMOSD.[10] However, recent evidence indicates NMOSD is usually associated with a specific biomarker, aquaporin-4 immunoglobulin-G (AQP4-IgG) antibody, which differentiates NMOSD from MS.[11] In the central nervous system aquaporins maintain neuroexcitatory processes and water homeostasis between the blood, cerebrospinal fluid and brain parenchyma.[12] Anti-AQP4-IgG antibodies trigger the complement cascade, which leads to inflammation and neuronal injury.[1] Modern assays detect anti-AQP4-IgG antibodies in approximately 80% of NMOSD patients.[13] Serum anti-AQP4-IgG antibody titers have been shown to correlate with NMOSD clinical disease activity, drop after immunotherapy, and remain low during remissions.[14] In addition, anti-AQP4-IgG antibody titers at the nadir of clinical attacks correlate with the length of longitudinally extensive spinal cord lesions.[14]

The prevalence of NMOSD is estimated at around 0.1 to 10 persons per 100,000 individuals, affecting approximately 15,000 individuals in the United States.[11] A 2019 to 2020 review of medical claims in the Oregon Medicaid population shows approximately 0.4 persons per 100,000 individuals have a diagnosis of NMOSD. NMOSD occurs in children and adults of all races, with a disproportionate prevalence among non-Caucasian females aged 30 to 40 years.[11] Danish and Caribbean-Africans appear to be at highest risk of being diagnosed with NMOSD.[15] The reported incidence of NMOSD in women is up to 10 times higher than in men.[16] It is difficult to determine exact prevalence rates as many NMOSD cases are never diagnosed and many others are misdiagnosed as MS.[10] A positive assay for anti-AQP4-IgG antibodies is not required for a definitive diagnosis of NMOSD.[8] Patients who test negative for anti-AQP4 antibodies, but meet clinical criteria for NMOSD, may have antibodies directed against other CNS proteins, and different lesion distributions.[8] NMOSD in patients that are AQP4 seronegative is poorly understood. This subset of patients may compromise a heterogenous population whose natural history and treatment response varies from NMSOD patients that are AQP4 seropositive.[8]

Patients with NMOSD may experience recurring relapses with accumulating disability which worsens with each relapse.[17] From the first attack, many patients with NMOSD suffer permanent and severe disability, irrespective of age at onset.[18] The risk of relapse is highest early in the course of the disease (~50 to 60% within the first year) and reported median time from onset attack to first relapse ranges from 8.5 to 14 months.[19] The vast majority of patients (80 to 90%) experience repeated relapses, and disability accumulates with each relapse.[17] Around 60% of patients relapse within 1 year of diagnosis and 90% relapse within 3 years.[9] Individuals who experience relapses, on average, have higher annual direct medical costs and indirect societal costs than those without relapse over the first year following diagnosis.[20] The negative impact of NMOSD on patient quality of life (QoL) is predominantly a result of physical disability, pain, vision impairment, and bladder dysfunction.[21] Disease-induced disability and symptoms have a considerable impact on patients' ability to work and thrive in social activities.[21] Historically, the loss of motor and sensory function leads to approximately 50% of patients to require a wheelchair and 62% of patients become functionally blind, within 5 years of diagnosis.[22]

The International Panel for NMO Diagnosis (IPND) was convened in 2011 to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus.[13] The IPND consisted of 18 members from 9 countries and was led by 2 co-chairs.[13] The panel agreed clinical diagnosis of NMOSD would be defined by integrating clinical, serologic, and neuroimaging data; diagnosis would not be based solely on detection of AQP4-IgG.[13] Revised consensus criteria published in 2015, base the diagnosis of NMOSD on anti-AQP4-IgG antibody status, magnetic resonance imaging (MRI) neuroimaging features, and the presence of at least 1 or more specific clinical characteristics.[13] The 6 core characteristics include:

- optic neuritis (eye pain, headache, blurred vision, color vision changes);
- acute myelitis (limb weakness or pain, spasticity of limbs or trunk, sensory disturbances);
- area postrema syndrome (unexplained hiccups or nausea and vomiting);
- acute brainstem syndrome (vomiting, hiccups, ocular movement disorders, pruritus, hearing loss, vertigo, facial palsy, trigeminal neuralgia) ;
- symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions;
- symptomatic cerebral syndrome with NMOSD-typical brain lesions.[13]

The panel concluded that criteria must define NMOSD in instances where AQP4-IgG serologic testing is negative or unavailable, especially because of the treatment implications.[13] Diagnostic requirements are more stringent for patients in whom AQP4-IgG is not detected or for whom testing is unavailable.[13] Such individuals must experience 2 or more different core clinical characteristics and other supportive MRI characteristics meant to enhance diagnostic specificity must also be present.[13]

The rationale for treatment of acute and recurrent attacks in NMOSD is based upon evidence that humoral autoimmunity plays a role in the pathogenesis of NMOSD, and is driven by the high attack-related disability, poor prognosis, and overall high risk of mortality in untreated patients.[15,23] Acute attacks are treated with high dose IV methylprednisolone (1 gram daily for 3 to 5 days) and may be followed with an oral prednisone taper.[15] Therapeutic plasmapheresis can be effective in patients with severe symptoms that fail to improve, or that progress despite treatment with corticosteroids.[15] The key treatment goal is long-term disease stabilization via a reduction in relapse risk and preventing potential permanent disability.[24] Many clinicians use immunosuppressants including azathioprine, methotrexate, mycophenolate, cyclophosphamide, rituximab, mitoxantrone or tocilizumab off-label to prevent NMOSD relapses.[25] Only 4 comparative randomized trials of immunosuppressants have been published.[26-29] Two trials were conducted in China,[28,29] 1 trial was in Japan,[27] and the other was completed in Iran.[26] Limited observational evidence suggests that treatment of NMOSD with interferon beta,[30] natalizumab,[31] or fingolimod[32] is not effective and may be harmful. For patients with NMOSD who are seropositive for AQP4-IgG antibodies, treatment can be initiated with newer medications such as eculizumab, inebilizumab, or satralizumab. Characteristics of the 3 products recently FDA-approved for treatment of NMOSD patients who are AQP4-seropositive are presented in **Table 1.**

Table 1. FDA-Approved Treatments for Neuromyelitis Optica Spectrum Disorder

	Eculizumab (Soliris®)	**Inebilizumab-cdon (Uplizna™)**	**Satralizumab-mwge (Enspryng™)**
Administration Route	Intravenous	Intravenous	Subcutaneous
Recommended NMOSD dose	**Loading Dose**: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 **Maintenance Dose**: 1200 mg every 2 weeks	**Loading Dose:** 300 mg at weeks 0, 2 **Maintenance Dose:** 300 mg every 6 months	**Loading Dose**: 120 mg at weeks 0, 2, 4 **Maintenance Dose**: 120 mg every 4 weeks
Primary Binding Target	Complement Protein C5	CD19 on B cells	Il-6 Receptor
Contraindications	Unresolved *Neisseria meningitides* infection Not vaccinated against *Neisseria meningitides*	Active Hepatitis B infection Active or Untreated Tuberculosis	Active Hepatitis B infection Active or Untreated Tuberculosis
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	None	None
Abbreviations: IL=interleukin; mg=milligram; NMOSD=Neuromyelitis Optica Spectrum Disorder; REMS = Risk Evaluation and Mitigation Strategies			

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 DRUG EVALUATION: Eculizumab (Soliris®)

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

Clinical Efficacy:

Eculizumab (Soliris®) is a recombinant humanized monoclonal antibody that blocks the cleavage of the terminal complement protein C5 into C5a and C5b, which subsequently inhibits the formation of the membrane attack complex.[1] The membrane attack complex is implicated in astrocyte destruction and neuronal injury.[1] Eculizumab is FDA-approved for 4 indications: 1) reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), 2) inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS), 3) treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive, and 4) treatment of NMOSD in adult patients who are anti-AQP4-IgG-antibody positive.[3] The FDA-approval for the use of eculizumab to treat NMOSD was granted June 2019. Recommended eculizumab dosing for NMOSD consists of a 900 mg loading dose administered via intravenous (IV) infusion once weekly for the first 4 weeks, followed by 1200 mg 1 week later, then 1200 mg every 2 weeks thereafter.[3] This summary will focus on evidence for use of eculizumab in treating NMOSD, and the other indications will be reviewed in the April 2021 class update of monoclonal C5 mediators.

A phase 3, double-blind, time-to-event, multicenter trial evaluated the safety and efficacy of eculizumab in adults with highly active AQP4-IgG seropositive NMOSD.[1] In the PREVENT trial, 143 patients were randomized 2:1 to receive either eculizumab or matched placebo. Patients required a history of 2 or more relapses in the 12 months prior to study enrollment or 3 relapses in the 24 months prior to enrollment and had an EDSS score of 7 or less.[1] Patients with an EDSS of 7 or less are unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hours a day.[2] Eculizumab was primarily add-on therapy: 78% of patients at baseline were receiving a stable-dose regimen of IST including chronic corticosteroids.[1] Eculizumab was initiated at a dose of 900 mg via IV infusion once weekly for 4 doses followed by 1200 mg every 2 weeks until first relapse, trial discontinuation, or the end of the trial.[1]

The primary end point was the number of adjudicated initial relapses compared to placebo.[1] Secondary outcomes included the annualized relapse rate and the score on the Expanded Disability Status Scale (EDSS), which ranges from 0 (no disability) to 10 (death).[1] Relapse was defined as any new onset or worsening of previous neurologic symptoms with an objective change on neurologic examination that persisted for 24 hours or more, was attributable to NMOSD, and was not due to an alternate identifiable cause such as an infection, excessive exercise, or high ambient temperature.[2] The treating physician made the determination of whether the event met the protocol definition of a relapse.[2] The treating physician determined the appropriate acute treatment for the relapse, including whether to change any concurrent IST.[2] The severity of the relapse was determined using the assessments as conducted by the treating physician.[2] An amendment to the study protocol established a relapse adjudication process in which a Relapse Adjudication Committee (RAC), composed of three neurologists or neuro-ophthalmologists external to the applicant and blinded to treatment assignment, would review all investigator-reported relapse events and a decision regarding whether a relapse would be deemed an on-trial protocol-defined relapse would be rendered by the RAC in a majority vote.[2] The treatment arm was observed for a median duration of 90 weeks and the placebo arm was observed for a median duration of 43 weeks.[1] The study sponsor terminated the study prematurely at 23 adjudicated relapses because there had been no relapses in the prior two years, and it was deemed it unnecessary to await the 24th relapse.[2] Patients who completed the trial to a relapse or trial termination were eligible to enter an extension study of open-label eculizumab treatment.

Moderate quality evidence shows adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (HR, 0.06; 95% CI, 0.02 to 0.20; P<0.001) over the follow-up period (median period: 90 weeks for active drug and 43 weeks for placebo).[1] A significant reduction in adjudicated annualized relapse rate was observed in patients treated with eculizumab compared with placebo (0.02 in the eculizumab group vs. 0.35 in the placebo group; RR, 0.045; 95% CI, 0.013 to 0.151; P<0.0001).[1] The mean change in the EDSS score (range 0 to 10) from baseline was not significantly different between the 2 treatment arms (–0.18 in the eculizumab group and 0.12 in the placebo group; LSMD, –0.29; 95% CI, –0.59 to 0.01).[1] The median change in EDSS was 0 for both treatment groups, and over 70% of eculizumab-treated patients had the same or experienced worsening of their EDSS scores at the end of study assessment.[2] Additional details of the PREVENT trial are described and evaluated below in **Table 4.**

Study Limitations:
The rationale for creating the RAC was to address an evident need for a more standardized approach to defining relapses due to "variability observed across sites in the diagnosis of relapse events."[2] This committee was convened after 93 patients had been randomized and 23 relapses had occurred, relatively late in the study progression.[2] The RAC adjudicated confirmation rates of the previously investigator-determined relapses differed between events in the eculizumab and placebo treatment groups and suggested a possible bias.[2] Ultimately, the treating investigators in the PREVENT trial reported 43 distinct relapse events in placebo-treated patients and 36 unique relapse events in eculizumab patients.[2] However, in the eculizumab-treated patients, the RAC confirmed just 8% (3/36) of investigator-reported relapses as protocol-defined relapses whereas the RAC confirmation rate for placebo treatment patients was 49% (21/43).[2] The FDA reviewer noted the 3 confirmed events (2 optic neuritis attacks and 1 myelitis attack) in eculizumab-treated patients were appropriately adjudicated as relapses whereas the other 33 events were nonspecific neurological symptoms or transient phenomena that did not meet the protocol definition of a relapse.[2] The FDA reviewer also notes that the 21 adjudicated relapses in the placebo group met the protocol definition of a relapse, tended to be more extensive, and were associated with greater symptom severity than the 3 relapses in the eculizumab group.[2] Therefore, the FDA concluded that the RAC-adjudicated relapses were appropriate to serve as the basis of the primary efficacy analysis.[2] Analyses of several of the secondary measures that were included to provide clinical readouts of ambulatory function and quality of life were described nominally, but did not trend toward improvement. However, the study was not designed in a manner that allows for an accurate estimation of disability and quality of life outcomes.[2] The time-to-event design of the trial meant that there was not a uniform observation duration for all enrolled patients.[2]

Clinical Safety:
Eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections which was identified in initial trials evaluating eculizumab use in other indications.[3] In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with eculizumab; both had been vaccinated.[3] In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient.[3] In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with eclulizumab.[3] All subjects enrolled in the PREVENT trial received immunization against meningococcal meningitis using regional vaccines.[2] No cases of meningococcal meningitis have been reported in adults with NMOSD.[2] Healthcare providers who prescribe eculizumab must enroll in the Solaris® Risk Evaluation and Mitigation Strategy (REMS) restricted program.[3] Prescribers must counsel patients about the risk of meningococcal infection, provide patients with REM educational materials, and ensure patients are immunized with meningococcal vaccine at least 2 weeks prior to starting therapy.[3] If urgent eculizumab therapy is warranted in an unvaccinated patient, the patient should begin a 2 week course of antibacterial drug prophylaxis.[3] Vaccination reduces, but does not eliminate, the risk of meningococcal infections.[3] Patients should be closely monitored for early signs and symptoms of meningococcal infection and evaluated immediately if an infection is suspected.[3]

The key risk of treatment with eculizumab is the risk of increased susceptibility to infections due to interference with the complement pathway.[2] Patients treated with eculizumab appeared to have a 1% higher risk of serious infections (most commonly, pneumonia) than placebo-treated patients.[2] This risk may be higher for infections with encapsulated organisms, most notably *Neisseria meningitidis*.[2] In the PREVENT trial, upper respiratory tract infections (29% vs. 13%), nasopharyngitis (21% vs. 19%), back pain (16% vs. 15%), and dizziness (15% vs. 13%) were more common in the eculizumab group compared with the placebo group.[1] There was one death from pulmonary empyema in the eculizumab group.[1] Infusion reactions were rare in the eculizumab group; only 2/96 (2%) patients experienced infusion reaction AEs that led to temporary study drug interruptions.[2] **Table 2** describes the adverse reactions experienced in 10% or greater of NMOSD patients treated with eculizumab.

Table 2. Adverse Reactions Reported in 10% or More of NMOSD patients treated with Eculizumab Compared with Placebo[3]

Adverse Events	Eculizumab (n=96)	Placebo (n=47)
Upper respiratory infection	29%	13%
Headache	23%	23%
Nasopharyngitis	21%	19%
Diarrhea	16%	15%
Dizziness	15%	13%
Back Pain	15%	13%
Arthralgia	11%	11%
Pharyngitis	10%	6%

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Annualized relapse rate
2) Disability and functional status
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in risk of relapse

Table 3. Pharmacology and Pharmacokinetic Properties[3]

Parameter	
Mechanism of Action	Complement protein C5 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of distribution: 5 to 8 L; Protein Binding N/R
Elimination	N/R

Half-Life	270 to 414 hours
Metabolism	N/R

Abbreviations: L=liters; N/A=not applicable; N/R=not reported

Table 4. 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.Pittock SJ, et al.[1] PREVENT trial DB, PC,PG, MC RCT	1. Eculizumab 900 IV mg every week for 4 weeks then 1200 mg every 2 weeks until relapse, trial discontinuation, or the end of the trial 2. Matched placebo administered at same dosing interval as eculizumab Trial was designed to continue until 24 patients had a NMOSD relapse. Trial terminated after 23 patients relapsed due to uncertainty when final event would occur. Median trial duration: 1. 90 weeks 2. 43 weeks	Demographics: -Mean annualized relapse rate in previous 24 mos: 1.99± 0.94 -Continued IST therapy:76% -Previous rituximab treatment: 32% -Gender: 91% female -Median age: 44 ±13 yrs -Median EDSS score: 4 (1.0 to 7.0) -Race: White:49% Asian: 37% Black: 12% Key Inclusion Criteria: -Adults ≥ 18 yo with a diagnosis of NMO or NMOSD -Anti-AQP4 antibody positive -At least 2 relapses in the last 12 mos or 3 relapses in the last 24 mos with at least 1 of those relapses occurring in the last 12 mos -EDSS score ≤ 7 -Maintained on stable IST dose prior to study admission Key Exclusion Criteria:	ITT: 1. 96 2. 47 PP: 1. 80 2. 44 Attrition: 1. 16 (17%) 2. 3 (6%)	Primary Endpoint: Number of subjects with adjudicated relapse in ITT population 1. 3 (3%) 2. 20 (43%) HR=0.06 95% CI, 0.02 to 2.0 P<0.001 Secondary Endpoints: A. Median time to first adjudicated relapse 1. Not Reached 2. 103 weeks B. Adjusted adjudicated Annualized Relapse Rate 1. 0.016 (0.01 to 0.05) 2. 0.350 (0.20 to 0.62) Rate Ratio=0.045 95% CI, 0.013 to 0.151 P<0.0001 C. Change from baseline in EDSS 1.-0.18 ± 0.81 2. 0.12 ± 0.95 LSMD = -0.29 95% CI, -0.59 to 0.01 P-value: NS	40%/3 NA NA NS	1.Any Adverse Event 1. 88 (92%) 2. 43 (91%) 2.Serious Adverse Events 1. 15 (16%) 2. 7 (15%) 3.Death 1. 1 (1%) 2. 0 (0%) 95% CI and p-values NR for all	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to eculizumab vs. placebo using IVRS. Stratified according to EDSS score (≤ 2.0 or 2.5-7.0 on 10 point scale) and use of concomitant IST (no therapy vs. maintenance therapy vs. new therapy). Baseline characteristics were similar between treatment groups, Performance Bias: Low. Patients, providers, and sponsor blinded to trial group assignments. Drug and placebo kits appeared identical. Detection Bias: Unclear. Treating MD evaluated relapse symptoms for first 88 patients. At that point, protocol modified to include independent, blinded adjudication committee to evaluate relapse symptoms. Attrition Bias: Unclear. Higher proportion of eculizumab patients discontinued trial participation (17% vs. 6%). Most of the eculizumab subjects who withdrew did so voluntarily for unknown reasons. Not related to treatment drug, relapses, or adverse events. Reporting Bias: Low. Protocol published online, all outcomes reported as outlined. Other Bias: High. Alexion designed and funded the trial. Study authors reported financial support from Alexion to support research, travel to steering committee meetings, consulting or employment. **Applicability**: Patient: -Median EDSS score of 4 indicated moderate disability. -Frequency of relapse was severe (2 attacks per year or 3 attacks in the previous 2 years). -Majority of patients were female, representative of population primarily impacted by NMOSD. -Only patients with AQP4 antibodies were included, cannot extrapolate findings to patients without AQP4 antibodies. Intervention: Dosing used in study reflects effective dosing identified in Phase 2 trials.

		-Use of rituximab or mitoxantrone 3 mos prior to screening -Use of IVIG 3 weeks prior to screening -Use of prednisone > 20 mg/day -Unresolved meningococcal disease						Comparator: Placebo comparator as no other FDA-approved treatments were marketed at the time of the study. Outcomes: Relapse rates are clinically appropriate endpoints for NMOSD. Setting: 70 sites in 18 countries Americas: 31% Europe: 36% Asia-Pacific: 33%

Abbreviations: AQP4=Aquaporin-4; ARR=Absolute Risk Reduction; DB=double-blind; CI confidence interval; EDSS=Expanded Disability Status Scale; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVRS=Interactive Voice Response System; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMO=Neuromyelitis Optica; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; PC=placebo-controlled; PG=parallel group; PP=per protocol; RCT=randomized clinical trial; yrs=years

NEW DRUG EVALUATION: Inebilizumab-cdon (Uplizna™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Inebilizumab-cdon (Uplizna™), is a humanized monoclonal antibody indicated for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive.[5] The antibody is afucosylated, which enhances antibody-dependent cellular cytotoxicity and improves therapeutic efficacy.[33] Inebilizumab is designed to bind the B cell-specific surface antigen CD19.[34] CD19 is expressed on a spectrum of B lymphocytes from pro-B cells to plasmablasts and is also present on some plasma cells.[34] B cells play an essential role in immune response to pathogens.[35] Binding of inebilizumab to CD19 results in depletion of B lymphocyte populations that express CD19.[34] Inebilizumab received FDA-approval in June 2020. Inebilizumab is also being studied for the treatment of myasthenia gravis, IgG4-releated disease, and kidney transplant patients with high levels of alloantibodies. The recommended inebilizumab dosing is 300 mg via IV infusion followed 2 weeks later by a second 300 mg IV infusion followed by 300 mg IV infusion every 6 months (starting 6 months from the first infusion).[5]

N-MOmentum was a phase 2/3 double-blind trial that evaluated the safety and efficacy of inebilizumab as monotherapy in reducing the risk of relapse and disability in adults with AQP4 seropositive or seronegative NMOSD.[4] Two hundred thirty participants were randomized 3:1 to inebilizumab or placebo at 99 clinical sites in 25 countries.[4] Ninety-three percent (n=213) of enrolled subjects were AQP4 seropositive.[4] Inebilizumab was administered as a 300 mg IV infusion dose on Days 1 and 15 of a 28-week randomized controlled period.[4] All patients also received oral corticosteroids (prednisone 20 mg/day or equivalent) between Days 1 and 14, tapered to Day 21, to minimize the risk of an NMOSD attack immediately following the first inebilizumab treatment.[4] No other use of immunosuppressants was permitted during the trial. The primary endpoint was to compare the efficacy of inebilizumab with placebo in reducing the risk of NMOSD attack in patients.[4] An attack was defined as the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMOSD that met the protocol-defined criteria for an attack upon neurological evaluation confirmed by an independent adjudication committee.[4] Secondary endpoints included worsening of EDSS score compared to baseline (increase of ≥2 from baseline of 0, increase of ≥1 from baseline of 1–5, or increase of ≥ 0.5 from baseline of ≥ 5.5), change in low-contrast visual acuity binocular (LCVAB) score from baseline, total number of active MRI-lesions, and number of NMOSD-related hospitalizations.[4] Lesion counts and hospitalizations were measured cumulatively up to the last visit of the randomized controlled period; disability worsening and visual acuity

were assessed at the last visit.[4] An open-label phase is ongoing, with 213 participants receiving inebilizumab every 26 weeks (162 participants from the original inebilizumab group and 51 participants from the original placebo group).[4]

The randomized controlled period was stopped before complete enrollment, as recommended by the independent data-monitoring committee, because of a clear demonstration of inebilizumab efficacy.[4] Moderate quality evidence showed 12% of (21/174) participants receiving inebilizumab in the intention-to-treat population had an attack versus 39% of (22/56) participants receiving placebo (HR, 0.272; 95% CI 0.150 to 0.496; p<0.0001) before day 197 of the trial.[4] Most attacks were myelitis and optic neuritis in both treatment groups.[4] Fewer attacks in the inebilizumab group compared with the placebo group were graded as major (28.6% vs. 45.5%, respectively).[4] In the AQP4 seropositive population, 11% (18/161) of patients receiving inebilizumab had an attack compared with 42% (22/52) of patients receiving placebo treatment (HR 0.227; 95% CI 0.121 to 0.423; p<0.0001).[4] Among the 17 AQP4-seronegative patients who were randomly allocated to treatment (13 to inebilizumab), three attacks occurred, all in the inebilizumab group.[4] Because only four AQP4-seronegative patients were randomly allocated to placebo and no attack occurred in this group, inebilizumab efficacy could not be interpreted in the AQP4-seronegative cohort.[4]

Fewer patients had EDSS score worsening from baseline with inebilizumab than with placebo (15.5% vs 33.9%; odds ratio [OR]: 0.370 95% CI: 0.1850 to 0.7389; p=0.0049).[4] Cumulative new MRI lesion count was significantly lower in inebilizumab-treated patients compared with placebo-treated patients (1.6 vs 2.3 lesions in the subgroup with lesions; RR: 0.566 for total number of new lesions; 95% CI: 0.387 to 0.828; p=0.0034).[4] Cumulative number of NMOSD-related hospitalizations was lower for inebilizumab-treated patients compared with placebo-treated patients (mean: 1.0 vs 1.4 for the subgroup with hospitalizations; RR: 0.286; 95% CI: 0.111 to 0.741; p=0.010).[4] There was no significant change (p=0.97) in low-contrast visual acuity form baseline as assessed by low-contrast Landolt C broken ring chart. Additional details of the N-Momentum trial are described and evaluated below in **Table 7**.

Study Limitations:
The study included only 17 AQP4 seronegative patients, representing 7% of the study population. Only four of these patients were in the placebo group, and they experienced no attacks.[4] Therefore, the efficacy of inebilizumab in AQP4 seronegative patients could not be determined.[4] Other study limitations include the variable observation periods between patients inherent in the time-to-event trial design (which also resulted in a significant amount of missing data), a consistent lack of relapse confirmation visits at an acceptable interval, and the protocol's inadequate approach to accounting for the impact of an acute relapse on EDSS changes from baseline.[34] The trial included a small study population and was of short duration (6 months). Post marketing trials are needed to assess long-term consequences of B-cell depletion (immunosuppression and opportunistic infections).[34] Although the trial was an international study that recruited patients from a wide range of backgrounds, inebilizumab has had little previous human exposure.[34] For safety reasons, patients with certain comorbidities or laboratory abnormalities were excluded.[4] Direct head-to-head trials have not been conducted between inebilizumab and immunosuppressive or immunological treatments currently used in clinical practice for NMOSD.[34]

Clinical Safety:
Across both the randomized and open-label treatment in the N-MOmentum trial, the most common adverse reactions (greater than or equal to 10%) were urinary tract infection (20%), nasopharyngitis (13%), infusion reaction (12%), arthralgia (11%), and headache (10%).[5] Inebilizumab can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other signs or symptoms.[5] During the randomized clinical trial period, infusion reactions were observed with the first course of inebilizumab in 9% of AQP4 seropositive NMOSD patients and 10% of patients in the placebo arm.[5] Infusion reactions were most common with the first infusion but were also observed during subsequent infusions.[5] Premedication with IV methylprednisolone 80mg to 125 mg, oral diphenhydramine 25mg to 50mg and oral acetaminophen 500 mg to 650 mg is recommended prior to each infusion to reduce the frequency and severity of infusion reactions.[5] Two deaths occurred in the inebilizumab cohort, but were not clearly attributable to active treatment.[34] Although

1 death was due to a brain lesion, it was not definitely proven to be due to progressive multifocal leukoencephalopathy (PML).[34] The drug label includes the presence of active infection as a contraindication to therapy and states that serious infections such as PML may occur during treatment with inebilizumab.[34] **Table 5** describes adverse reactions reported in 5% or greater of patients with AQP4 seropositive NMOSD compared to placebo.

Table 5. Adverse Reactions in Patients with NMOSD with an Incidence of Least 5% with Inebilizumab Compared with Placebo[5]

Adverse Reaction	Inebilizumab (N=161)	Placebo (n=52)
Urinary Tract Infection	11%	10%
Arthralgia	10%	4%
Headache	8%	8%
Back Pain	7%	4%

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Annualized relapse rate
2) Disability status as evaluated by the EDSS
3) Functional status
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in risk of relapse

Table 6. Pharmacology and Pharmacokinetic Properties[5]

Parameter	
Mechanism of Action	CD19 B-cell binder
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of distribution: 2.95 L (central) and 2.57 L (peripheral); Protein Binding N/R
Elimination	Total body clearance: 0.19 L/day
Half-Life	18 days
Metabolism	Degraded by proteolytic enzymes throughout the body

Abbreviations: L=Liters; N/A=Not Applicable; NR=Not Reported

Table 7. 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. Cree, BAC, et al.[4] N-MOmentum DB, PC, MC RCT	1. Inebilizumab 300 mg IV on Days 1 and 15 2. Placebo IV on days 1 and 15 197 days (6.5 months) follow-up	Demographics: - Anti-AQP4 antibody positive:93% - No prior NMOSD therapy: 33% - Previous treatment: corticosteroid: 45% rituximab: 7% - Gender: 91% female - Median age: 43 yr - Median baseline EDSS score: 4 (Range:1-8) - Race: White:52% Asian: 18% Black: 9% Hispanic: 20% Key Inclusion Criteria: - Adults ≥ 18 yo with a diagnosis of NMOSD - AQP4 seropositive or seronegative - At least ≥ 1 relapse requiring rescue therapy in the 12 mos or ≥ 2 relapses requiring rescue therapy in the 24 mos prior to screening - EDSS score ≤ 8 Key Exclusion Criteria: - Use of alemtuzumab, bone marrow transplant, T-cell vaccination therapy, or total lymphoid irradiation at any time - Use of rituximab ≤ 6 mos prior to screening - Use if IVIG ≤ 4 weeks prior to screening - Use of natalizumab, tocilizumab, cyclosporine, methotrexate, mitoxantrone, eculizumab, or cyclophosphamide ≤3 mos prior to screening - Use of prednisone >20 mg/day	ITT: 1.174 2. 56 PP: 1.169 2. 54 Attrition: 1. 5 (3%) 2. 2 (4%)	Primary Endpoint: Number of subjects with relapse in ITT population 1. 21 (12%) 2. 22 (39%) HR 0.272 95% CI, 0.150 to 0.496 P<0.0001 Secondary Endpoints: A. Number of patients with worsening EDSS from baseline in ITT population 1. 27 (16%) 2. 19 (34%) OR 0.370 95% CI 0.185 to 0.739 P= 0.0049 B. Number of patients with a change from baseline in LCVAB score in ITT population 1. 171 2. 56 LSMD 0.134 95% CI, -2.025 to 2.294 P=0.90 C.Cumulative number of active MRI lesions in ITT population 1. 79 2. 32 RR 0.566 95% CI, 0.387 to 0.828 P=0.0034 D.Cumulative number of NMOSD-related hospitalizations from baseline in ITT population	26%/4 18%/6 NS NA	Adverse Effects in ITT population 1. 125 (72%) 2. 41 (73%) Serious Adverse Effects in ITT population 1. 8 (5%) 2. 5 (9%) Serious Adverse Effect Leading to Treatment Discontinuation in ITT population 1. 2 (1%) 2. 0 (0%) 95% CI and p-values NR for all	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 3:1 to inebilizumab or placebo via IVRS. Stratified by AQP4 status. Baseline characteristics were similar in both treatment groups. Performance Bias: Low. Participants, investigators, and all clinical staff were masked to treatment assignment. Detection Bias: Low. Treatment drug and placebo were similar in appearance. Relapse adjudication committee were independent providers. Attrition Bias: Low. Attrition was low in both groups. Reporting Bias: Low. Protocol published online, all outcomes reported as outlined. Other Bias: High. Funded by MedImmune and Viela Bio. Employees of MedImmune and Viela Bio participated in the design and conduct of the study, data collection, management, analysis, and interpretation. **Applicability**: Patient: 91% of subjects were female. 52% of subjects were white, which is not reflective of NMOSD ethnic prevalence. 33% were naïve to previous NMOSD therapy. Intervention: Two-dose assessment in randomized period shown effective in phase 1 trials. Comparator: Placebo comparator selected as there are no other approved NMOSD therapies. Ethics of treating NMOSD patients with placebo contributed to challenges in recruiting eligible subjects. Randomizing 3:1 treatment to placebo helped reduce enrollment of subjects in the placebo arm. Outcomes: Relapse and disability are reasonable outcomes to evaluate NMOSD. Setting: 25 countries including: Australia, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Germany, Hong Kong, Hungary, Israel, Japan, Mexico, Moldova, New Zealand, Peru, Poland, Russia, Serbia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, and USA.

		- Active severe bacterial, viral, or other infection - History of hepatitis B and/or hepatitis C		1. 10 2. 8 RR 0.286 95%CI, 0.111 to 0.741 P=0.010	NA			

Abbreviations: AQP4=Aquaporin-4; DB= double-blind; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVIG= intravenous immunoglobulin; IVRS=Interactive Voice Response System; LCVAB=Low-Contrast Visual Acuity Binocular; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; OR=odds ratio; PC=placebo-controlled; PP=per protocol; RR=rate ratio; RCT=randomized clinical trial; USA=United States of America; yo=years old; yrs=years

NEW DRUG EVALUATION: Satralizumab-mwge (Enspryng™)

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:

Satralizumab-mwge (Enspryng™) is a recombinant, humanized monoclonal antibody indicated for the treatment of NMOSD as monotherapy or in combination with IST in adult patients who are anti-AQP4 antibody positive.[36] Satralizumab prevents interleukin-6 (IL-6) from binding and inhibits IL-6 receptor signaling.[6] IL-6 promotes the differentiation of naïve T cells into inflammatory T-helper-17 cells, which stimulate the differentiation of B cells into plasmablasts that produce AQP4-IgG.[6] IL-6 increases the permeability of the blood–brain barrier, allowing penetration of AQP4-IgG and proinflammatory cells into the CNS.[37] Satralizumab received FDA breakthrough therapy designation in December 2018 for the treatment of NMOSD. Dosing begins with 120 mg subcutaneously (SC) self-administered every 2 weeks for the first 3 doses and then every 4 weeks thereafter.[36] The safety and efficacy of satralizumab in NMOSD patients were evaluated in two phase 3, randomized, placebo-controlled, multicenter, double-blinded studies with open-label extensions.[6,7] In both studies, the primary endpoint was evaluated in the intent-to-treat (ITT) population, consisting of both AQP4 seropositive and AQP4 seronegative patients, and measured the time to first relapse.[6,7] SAkuraSky[6] investigated satralizumab added to baseline IST in adolescents and adults, while SakuraSTar[7] evaluated satralizumab monotherapy in adults. Enrollment of AQP4 seronegative patients was limited to 30% in both trials to reflect estimated prevalence in the NMOSD population.

In the SAkuraSky trial, satralizumab was added to stable baseline azathioprine (AZA), mycophenolate mofetil (MMF), or glucocorticoids in adults aged 18 years and older.[6] In adolescents aged 12 to 17 years (n=7), satralizumab was added to AZA or MMF in combination with glucocorticoids.[6] No other baseline IST was permitted. Eighty-three patients were randomized 1:1 to satralizumab 120 mg SC or placebo, given at Weeks 0, 2, 4, and every four weeks thereafter, in addition to their baseline IST treatment.[6] The primary end point was the first PDR in a time-to-event analysis.[6] Relapses were defined via protocol as new or worsening objective neurological symptoms with at least one of the following:

- increase of 1.0 or more EDSS points from a baseline EDSS score of more than 0 (or increase of ≥ 2.0 EDSS points from a baseline EDSS score of 0);
- increase of 2.0 or more points on at least one appropriate symptom-specific functional system score;
- increase of 1.0 or more points on two or more symptom-specific functional system scores with a baseline of at least 1.0;
- or increase of 1.0 or more points on a single-eye symptom-specific functional system score with a baseline score of at least 1.0.[6]

Symptoms were required to be attributable to NMOSD, persisting for more than 24 hours, and not attributable to confounding clinical factors such as fever, infection, injury, change in mood, or adverse reactions to medications.[6] Relapses were adjudicated by an independent Clinical Endpoint Committee (CEC) masked to treatment assignment. Key secondary end points were the change from baseline to week 24 in the visual-analogue scale (VAS) pain score (range, 0 to

100, with higher scores indicating more pain) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (range, 0 to 52, with lower scores indicating more fatigue).[6] Evidence with other IL-6 antagonists has demonstrated reduction in pain and fatigue.[6]

Among patients who received satralizumab, 20% (n=8) experienced a PDR compared with 43% (n=18) of patients who received placebo (HR 0.38; 95% CI, 0.16 to 0.88; p=0.02) at 48 weeks.[6] In AQP4-IgG seropositive patients, 11% of satralizumab-treated patients experienced a PDR at week 48 compared with 43% of placebo-treated patients (HR=0.66; 95% CI: 0.06-0.75; p=0.0086).[6] There was no significant difference in relapse risk reduction for AQP4-IgG seronegative patients treated with satralizumab (n=14) versus placebo (n=14).[6] The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.[6]

In the SAkuraStar trial, satralizumab was evaluated as monotherapy in patients 18 to 74 years of age (N=95) at 44 sites in 13 countries.[7] Eligible participants had experienced at least one documented NMOSD attack or relapse in the past 12 months and had a score of 6.5 or less on the EDSS.[7] Exclusion criteria included clinical relapse 30 days or fewer before baseline.[7] Patients were randomized 2:1 to satralizumab 120 mg SC or placebo, given at Weeks 0, 2, 4, and every four weeks thereafter.[7] Taking immunosuppressants (i.e. AZA or MMF) concomitantly was prohibited.[7] Corticosteroids and intravenous immunoglobulin were also prohibited except as rescue therapy; rescue therapy (e.g., pulse intravenous corticosteroids) was permitted for treatment of relapse.[7] The primary endpoint was time to the first PDR, based on the intention-to-treat population and analyzed with stratification for two randomization factors (previous therapy for prevention of attacks and nature of the most recent attack).[7] Protocol-defined relapses were similar to the parameters used in the SAkuraSky trial. Relapses were adjudicated by a Clinical Endpoint Committee (CEC) masked to treatment assignment. The double-blind phase was due to last until 44 protocol-defined relapses occurred or 1.5 years after random assignment of the last patient enrolled, whichever occurred first; participants could enter an open-label phase after the occurrence of a protocol-defined relapse or at the end of the double-blind phase.[7] Key secondary end points were the change from baseline to week 24 in VAS pain score and the FACIT-F score. Additional predefined secondary outcomes were the proportion of relapse-free patients.[7]

Protocol-defined relapses occurred in 19 (30%) patients receiving satralizumab and 16 (50%) receiving placebo (HR 0.45, 95% CI 0.23 to 0.89; p=0.018).[7]
In AQP4-IgG seropositive patients, satralizumab showed a 74% reduction in the risk of relapse (HR=0.26; 95% CI: 0.11 to 0.63).[7] The key secondary QoL outcome measures, change in baseline pain on the VAS and functional assessment of chronic fatigue on the FACIT-F scores, were not significantly different between treatment groups.[7]

Trial Limitations
Satralizumab reduced the risk of relapse in patients who were AQP4-IgG seropositive; however, there is insufficient evidence to indicate a risk reduction for the AQP4-IgG seronegative subgroup.[7] The absence of observed efficacy in seronegative patients might be partly attributable to the greater degree of disease heterogeneity within the general AQP4-IgG seronegative subpopulation, as well as the small sample size.[7] The study was not designed or powered to detect differences in efficacy within these subgroups.[7] Findings from the SAKuraSky trial were not adequate to support any conclusions regarding satralizumab efficacy or safety in the adolescent population.[7] Additional details of the 2 trials are described and evaluated below in **Table 11.**

Clinical Safety:
The most common risks of treatment with satralizumab were an increased risk of several types of infections (nasopharyngitis, upper respiratory tract infection) headache, rash, arthralgia, extremity pain, fatigue, and nausea. Other IL-6 antagonists (sarilumab and tocilizumab) have boxed warnings for serious infections and potential tuberculosis or hepatitis B reactivation.[8] No cases of tuberculosis or hepatitis B were reported in satralizumab clinical trials because these patients were excluded. Injection site reactions occurred approximately 3% more often in satralizumab-treated patients compared with placebo.[8] No deaths or

anaphylactic reactions were observed with satralizumab. Additional details regarding adverse events observed in the SAkuraStar and SAkuraSky trials are described in **Table 8** and **Table 9,** respectively.

Table 8. Adverse Reactions in Patients with NMOSD with an Incidence of Least 10% with Satralizumab Monotherapy Compared with Placebo[36]

Adverse Reaction	Satralizumab (n=41)	Placebo (n=23)
Rash	17%	0%
Arthralgia	17%	0%
Pain in Extremity	15%	9%
Fatigue	15%	4%
Nausea	15%	9%
Nasopharyngitis	12%	4%
Pruritus	10%	0%
Depression	10%	0%
Cellulitis	10%	0%
Neutropenia	10%	4%
Increased blood phosphokinase	10%	4%
Fall	10%	4%

Table 9. Adverse Reactions in Patients with NMOSD with an Incidence of Least 10% with Satralizumab and IST Compared with Placebo and IST[36]

Adverse Reaction	Satralizumab + IST (n=26)	Placebo + IST (n=26)
Nasopharyngitis	31%	15%
Headache	27%	12%
Upper respiratory tract infection	19%	12%
Gastritis	15%	0%
Arthralgia	12%	0%
Pharyngitis	12%	8%

Abbreviations: IST=Immunosuppressant Therapy

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Annualized relapse rate
2) Reduction in pain as evaluated by VAS
3) Reduction in fatigue as evaluated by FACIT-F score
4) Functional status
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

2) Reduction in risk of relapse

Table 10. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	IL-6 antagonist
Subcutaneous Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 3.46 L (central) and 2.07 L (peripheral); Protein Binding N/R
Elimination	Clearance: 0.0601 L/day
Half-Life	30 days
Metabolism	Degraded by proteolytic enzymes throughout the body

Abbreviations: IL=interleukin; L=Liters; N/A=not applicable; N/R=Not Reported

Table 11. 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. Yamamura T, et al.[6] SAkuraSky DB, PC, PG MC, Phase 3 RCT	1. Satralizumab 120 mg SC added to IST at weeks 0, 2, 4, and every 4 weeks thereafter 2. Matched placebo added to IST administered SQ at week 0, 2, 4 and every 4 weeks thereafter Median trial duration: 1. 107 weeks (2-224) 2. 32.5 weeks (0-180)	Demographics: -Anti-AQP4 antibody positive: 63% -Female: 93% -Median age: 45.5 yrs -Age < 18 yo: 8% Race: White: 61% Asian: 39% Key Inclusion Criteria: 1. Patients aged 12-74 yrs with NMOSD 2. AQP4 seropositive or seronegative 3. Stable AZA, MMF, or OCS therapy dose at least 8 wks prior to screening 4. At least 2 relapses in the 24 mos prior to screening with at least 1 relapse occurring within 12 mos prior to screening 5. EDSS score $\leq$ 6.5 Key Exclusion Criteria: 1. Any prior treatment with an IL-6 inhibitor, alemtuzumab, total lymphoid irradiation, or bone marrow transplant 2. Anti-CD20 therapy, eculizumab, anti-B-lymphocyte stimulator monoclonal antibody, or any other MS disease-modifying treatment within 6 mos prior to screening 3. Anti-CD4, cladribine, or mitoxantrone within 2 years	ITT: 1. 41 2. 42 PP: 1. 38 2. 32 Attrition: 1. 3(7%) 2.10 (24%)	Primary Endpoint: Number of patients with a protocol defined relapse in ITT population at week 48 1. 8 (20%) 2. 18 (43%) HR 0.38 95% CI, 0.16 to 0.88; P=0.02 Secondary Endpoints: A. Percent of AQP4 seropositive subjects with protocol defined relapse 1. 3 (11%) (n=27) 2. 12 (43%) (n=28) HR 0.21 95% CI 0.06 to 0.75; P=0.0086 B. Percent of AQP4 seronegative subjects with protocol defined relapse 1. 5 (36%) (n=14) 2. 6 (43%) (n=14) HR 0.66 95% CI 0.20 to 2.24; P=NS C. Change in mean VAS pain score from baseline at 24 weeks in ITT population 1. 2.87 2. -3.51 Difference: 6.38 95% CI = -0.28 to 13.03; P=0.0932 D. Change in mean FACIT-F score from baseline to week 24 in ITT population 1. 0.14 2. 2.23 Difference: -2.09 95% CI = -4.75 to 0.57; P=0.0983	23%/5 32%/4 NS NS NS	1.Adverse Events 1. 37 (90%) 2. 40 (95%) 2.Serious Adverse Events 1. 7 (17%) 2. 9 (21%) 3. Infections 1. 28 (68%) 2. 26 (62%) 4. Injection-related Reactions 1. 5 (12%) 2. 2 (5%) 95% CI and p-value NR	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 to satralizumab or placebo. Stratified by baseline annualized relapse rate (1 vs. >1) and geographic region (Asia, North America or Europe). Method of randomization not described. Baseline characteristics were balanced between treatment groups except for overall number of patients using AZA (n=29) vs. MMF (n=12) vs. OCS (37). Performance Bias: Low. Patients and all study personnel blinded to treatment assignment. Placebo matched in appearance to active drug. Detection Bias: Low. Relapse symptoms assessed independently from the treating provider. Attrition Bias: Unclear. More attrition in placebo cohort due to ADE (12%) vs active drug (7%). Reporting Bias: Low. Protocol published online, all outcomes reported as outlined. Other Bias: (high) Funded by Funded by Chugai Pharmaceutical (Roche). Employees of Roche participated in the design and conduct of the study, data collection, management, analysis, and interpretation. **Applicability**: Patient: Age range included adolescents. Enrollment of AQP4 seropositive and seronegative subjects capped to reflect proportion of subjects in overall population. Intervention: Dosing used in study reflects effective dosing identified in Phase 2 trials. Comparator: Placebo selected as comparator as no other FDA-approved treatments were marketed at the time of the study. Outcomes: Relapse rates are clinically appropriate endpoints for NMOSD. Setting: 34 clinical sites in 11 countries: France (n=1) Germany (n=3) Hungary (n=2) Italy (n=9) Japan (n=22) Poland (n=23) Spain (n=2) Taiwan (n=12) Ukraine (n=3) United Kingdom (n=2) United States (n=1)

2. Traboulsee A, et al.[7] SAkuraStar DB, PC, PG, MC, Phase 3 RCT	1. Satralizumab monotherapy 120 mg SC at weeks 0, 2, 4, and every 4 weeks thereafter 2. Matched placebo administered SQ at week 0, 2, 4 and every 4 weeks thereafter Median Treatment Duration: 1. 92 weeks (0-202 weeks) 2. 55 weeks (2-216) Trial ended after 35 PDRs observed over 1.5 years	Demographics: -Anti-AQP4 antibody positive: 70% -Female: 81% female -Median age: 43 yr -Race: White: 65% Asian: 15% -Mean EDSS score: 3.8 Key Inclusion Criteria: 1. Adults aged 18 to 74 yrs with NMOSD 2. AQP4 seropositive or seronegative 3. At least 1 relapse in the 12 mos prior to screening 4. EDSS score $\leq$ 6.5 Key Exclusion Criteria: 1. Concomitant IST therapy 2. Relapse 30 days or less before study enrollment 3. Any prior treatment with an IL-6 inhibitor, alemtuzumab, total lymphoid irradiation, or bone marrow transplant 4. Anti-CD20 therapy, eculizumab, anti-B-lymphocyte stimulator monoclonal antibody, or any other MS disease-modifying treatment within 6 mos prior to screening 5. Anti-CD4, cladribine, or mitoxantrone within 2 years	ITT: 1. 63 2. 32 PP: 1. 56 2. 28 Attrition: 1. 7 (11%) 2. 4 (13%)	Primary Endpoint: Number of patients with a protocol defined relapse in ITT population at week 48 1.19 (30%) 2.16 (50%) HR 0.45 95% CI, 0.23 to 0.89 P=0.018 Secondary Endpoints: A. Percent of AQP4 seropositive subjects with protocol defined relapse 1. 5 (11%) n=41 2. 10 (43%) n=23 HR 0.21 95% CI 0.06 to 0.75 p-value NR B. Change from baseline in VAS score for pain at 24 wks 1. -2.74 2. -5.95 P=0.44 C. Change in mean FACIT-F score from baseline to week 24 in ITT population 1. 5.71 2. 3.60 P=NS D. Annualized Relapse Rate in ITT population 1. 0.2 2. 0.4 Difference 0.2 95% CI, 0.21 to 0.79 p-value NR	20%/5 32%/4 NS NS NA	1. Adverse Events 1. 58 (92%) 2. 24 (75%) 2. Serious Adverse Events 1. 12 (19%) 2. 5 (16%) 3. Infections 1. 34 (54%) 2. 14 (44%) 4. Injection-related Reactions 1. 8 (13%) 2. 3 (9%) 95% CI and p-value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 2:1 to satralizumab or placebo via IVRS. Subjects stratified by previous IST (B cell depletion vs. other IST) and nature of most recent symptoms (attack vs. relapse). Baseline demographics were balanced between treatment groups except for male gender (27% in treatment group vs. 3% in placebo group). Performance Bias: Low. Patients and all study personnel blinded to treatment assignment. Placebo matched in appearance to active drug. Detection Bias: Low. Relapse symptoms assessed separately from the treating investigator. Attrition Bias: Low. Attrition rates similar between treatment groups. Reporting Bias: Low. Protocol published online, all outcomes reported as outlined. Other Bias: High. Funded by Funded by Chugai Pharmaceutical (Roche). Employees of Roche participated in the design and conduct of the study, data collection, management, analysis, and interpretation. **Applicability**: Patient: Enrollment of AQP4 seropositive and seronegative subjects capped to reflect proportion of subjects in overall population. Intervention: Dosing used in study reflects effective dosing identified in Phase 2 trials. Comparator: Placebo selected as comparator as no other FDA-approved treatments were marketed at the time of the study. Outcomes: Relapse rates are clinically appropriate endpoints for NMOSD. Setting: 44 clinical sites in 13 countries: Bulgaria, Canada, Croatia, Georgia, Italy, Malaysia, Poland, Romania, South Korea, Taiwan, Turkey, United States, and Ukraine.

Abbreviations: AQP4=Aquaporin-4; ARR=Absolute Risk Rediction; AZA=azathioprine; DB= double-blind; CI=confidence interval; EDSS=Expanded Disability Status Scale; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HR=Hazard Ratio; IST=immunosuppressive therapy; ITT=intention to treat; IV=intravenous; IVRS=Interactive Voice Response System; LCVAB=Low-Contrast Visual Acuity

Binocular; LSMD=Least Squares Mean Difference; MC=multi-center; mg=milligram; MMF = mycophenolate mofetil; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NMOSD=Neuromyelitis Optic Spectrum Disorder; NS=Not Significant; OCS=oral corticosteroid therapy; OR=odds ratio; PC=placebo-controlled; PG=parallel group; PP=per protocol; RR=rate ratio; RCT=randomized clinical trial; VAS= Visual Acuity Score; wks=weeks; yo=year old; yrs=years

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Appendix 1: Current Preferred Drug List

Class	Generic	Brand	Route	Form	PDL
Biologics for Rare Diseases	eculizumab	SOLIRIS	IV	VIAL	
Biologics for Rare Diseases	inebilizumab-cdon	UPLIZNA	IV	VIAL	
Biologics for Rare Diseases	satralizumab-mwge	ENSPRYNG	SUB-Q	SYRINGE	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2, 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 15, 2021

1.	*exp Neuromyelitis Optica/*	*2806*
2.	*inebilizumab.mp.*	*29*
3.	*eculizumab.mp.*	*1792*
4.	*satralizumab.mp*	*20*
5.	*2 or 3 or 4*	*1812*
6.	*1 and 5*	*26*

Appendix 3: Prescribing Information Highlights

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

SOLIRIS® (eculizumab) injection, for intravenous use
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection.)**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

  Limitation of Use
  Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive (1.3).
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG and NMOSD Dosage Regimen: (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.1).
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain (6.1).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

UPLIZNA™ (inebilizumab-cdon) injection, for intravenous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

UPLIZNA is a CD19-directed cytolytic antibody indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, quantitative serum immunoglobulins, and tuberculosis screening is required before the first dose (2.1)
- Prior to every infusion:
  - Determine if there is an active infection (2.2, 5.2)
  - Premedicate with a corticosteroid, an antihistamine, and an antipyretic (2.2, 5.1)
- UPLIZNA must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP prior to administration (2.3, 2.4)
- UPLIZNA is administered as an intravenous infusion titrated to completion, approximately 90 minutes. The recommended dose is:
  - Initial dose: 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion
  - Subsequent doses (starting 6 months from the first infusion): single 300 mg intravenous infusion every 6 months (2.3)
- Monitor patients closely during the infusion and for at least one hour after completion of the infusion (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

- Previous life-threatening reaction to infusion of UPLIZNA (4)
- Active hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infusion reactions: Administer premedications prior to infusion (2.2) Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue UPLIZNA if a life-threatening or disabling infusion reaction occurs (5.1)
- Infections: Delay UPLIZNA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion (5.2)
- Immunoglobulin levels: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion. Consider discontinuing UPLIZNA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise (5.3)
- Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA (5.4, 8.1)

ADVERSE REACTIONS

The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Viela Bio, Inc. at 1-855-558-4352 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 6/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ENSPRYNG™ (satralizumab-mwge) injection, for subcutaneous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

ENSPRYNG is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, tuberculosis, and liver transaminase screening is required before the first dose. (2.1)
- Prior to every use, determine if there is an active infection. (2.2)
- The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks. (2.2)
- See Full Prescribing Information for important preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Known hypersensitivity to satralizumab or any of the inactive ingredients (4)
- Active Hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infections: Delay ENSPRYNG administration in patients with an active infection until the infection is resolved. Vaccination with live or live-attenuated vaccines is not recommended during treatment. (5.1)
- Elevated Liver Enzymes: Monitor ALT and AST levels during treatment; interruption of ENSPRYNG may be required. (5.2)
- Decreased Neutrophil Counts: Monitor neutrophils during treatment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 15%) are nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

Eculizumab (Soliris®)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is FDA-approved for:
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
  - Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AchR) antibody positive

Length of Authorization:

Up to 12 months

Requires PA:

- Soliris® (eculizumab) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Has the patient been vaccinated against *Neisseria meningitides?*	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis one of the following: • Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), OR • atypical Hemolytic Uremic Syndrome (aHUS)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the requested dosing align with the FDA- approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for a diagnosis of myasthenia gravis (MG) ACh Receptor (AChR) antibody-positive?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient tried: • at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR • at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab[1]

	Eculizumab (Soliris®)
FDA-approved Indications	• Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody • Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) • Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive
Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter
Recommended aHUS dose in patients less than 18 yo	Weight based: refer to prescribing information for dosing in pediatric patients
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter
Recommended generalized MG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter

Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)

1. Soliris (eculizumab) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 4/21 (DM)
Implementation: TBD

Inebilizumab-cdon (Uplizna™)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

Up to 12 months

Requires PA:

- Uplizna™ (Inebilizumab-cdon) 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 the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 4
4. Is the request for Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been screened for Hepatitis B and tuberculosis infection?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/21 (DM)
Implementation: TBD

Satralizumab-mwge (Enspryng™)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:
Up to 12 months

Requires PA:
- Enspryng™ (Satralizumab-mwge) pharmacy 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 4
4. Is the request for Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Has the patient been screened for Hepatitis B and tuberculosis infection?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/21 (DM)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update and Drug Evaluation: Monoclonal C5 Inhibitors

Date of Review: April 2021

Dates of Literature Search: 01/01/1996-01/20/2021

Generic Name:
Eculizumab
Ravulizumab-cwvz

Brand Name (Manufacturer):
Soliris® (Alexion Pharmaceuticals)
Ultomiris® (Alexion Pharmaceuticals)

Dossier Received: yes

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

Purpose for Class Update:
To define place in therapy for 2 immunosuppressive agents, eculizumab and ravulizumab. Eculizumab is FDA-approved for 4 indications including: 1) reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), 2) inhibiting complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic-uremic syndrome (aHUS), 3) managing generalized myasthenia gravis (MG) and 4) treatment of adults with neuromyelitis optica spectrum disorder (NMOSD). Management of NMOSD is reviewed in a separate Pharmacy & Therapeutics Committee review. Ravulizumab is FDA-approved for treatment of PNH and aHUS.

Research Questions:
1. What is the effectiveness of eculizumab in reducing hemolysis in patients with PNH, inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS, and managing generalized MG?
2. What are the harms of eculizumab in adults with PNH, aHUS and MG?
3. What is the efficacy of ravulizumab in reducing hemolysis in patients with PNH and inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS?
4. What are the harms of ravulizumab in adults with PNH and aHUS?
5. Is there comparative evidence that eculizumab and ravulizumab differ in efficacy or harms for management of PNH and aHUS?
6. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which eculizumab or ravulizumab may be beneficial or cause more harm?

Author: Deanna Moretz, PharmD, BCPS

Conclusions:

Eculizumab

- The efficacy and safety of eculizumab in adults with PNH was demonstrated in 2 multinational, phase 3 trials. In the double-blind Transfusion Reduction Efficacy and Safety Clinical Investigation (TRIUMPH), patients with severe PNH disease (n=87) were randomized to eculizumab or placebo and evaluated over 26 weeks.[1] The open-label, single-arm, 52 week Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (SHEPHERD) trial evaluated eculizumab in a broader PNH patient population (e.g., patients with thrombocytopenia and mild anemia; n=97).[2]
- Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in lactate dehydrogenase (LDH) is common in classic PNH.[3] The co-primary endpoints in the TRIUMPH trial were the stabilization of hemoglobin levels and the number of units of packed red cells transfused.[1] Low-quality evidence showed stabilization of hemoglobin levels and the requirement for packed red cell transfusions were improved significantly more with eculizumab than with placebo after 26 weeks of treatment.[1] Forty-nine percent of all patients in the eculizumab group were transfusion independent compared with 0% of patients in the placebo group ($p<0.001$).[1] In the SHEPHERD trial, eculizumab significantly reduced requirements for packed red cell transfusions throughout the study.[2] During 52 weeks of eculizumab therapy, the median number of units transfused per patient was 0 compared with 8 units in the year prior to treatment ($p<0.001$; low-quality evidence).[2]
- In the TRIUMPH trial, hemolysis was also significantly reduced with eculizumab compared with placebo, as determined by lower mean levels of LDH in the eculizumab treatment group (low-quality evidence).[1] The median area under the concentration-time curve (AUC) for LDH was 86% lower with eculizumab than with placebo (58,587 vs. 411,822 U/L per day respectively; $p < 0.001$; low-quality evidence).[1] In the SHEPHERD trial, hemolysis was significantly improved from baseline with eculizumab treatment, as demonstrated by the reduction in LDH AUC (median change -632,264 IU/L per day; $p<0.001$; low quality evidence) after 52 weeks of treatment.[2] Mean LDH was significantly reduced by 87%, from 2201 IU/L at baseline to 297 IU/L at week 52 ($p<0.001$; low quality evidence).[2]
- The randomized, placebo-controlled, double-blind, multicenter, phase 3 REGAIN study evaluated the safety and efficacy of eculizumab in adults with MG.[4] The primary efficacy endpoint was the change from baseline to week 26 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score according to a prespecified worst-rank ANCOVA strategy.[4] The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank 56.6 vs. 68.3; rank-based treatment difference −11.7; 95% CI −24.3 to 0.96; $p=0.0698$; moderate-quality evidence).[4]
- Two, single-arm, multinational, 26-week, phase 2 trials evaluated intravenous eculizumab inhibition of complement-mediated thrombotic microangiopathy (TMA) in patients aged 12 years and older with aHUS.[5] Complete TMA response was defined as hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine in two consecutive measurements for four or more weeks).[5] Trial C08-002 included patients with progressive TMA who were refractory to plasma exchange or infusion while Trial C08–003 included patients with chronic dependence on plasma exchange or infusion.[5] At week 26, 65% and 25% of patients demonstrated complete TMA response in both trials (low-quality evidence).[5] At 26 weeks, the platelet count was significantly increased from baseline in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, and thrombotic microangiopathic event-free status was achieved in 80% of patients with a long disease duration and chronic kidney disease who received long-term plasma exchange/infusion (low-quality evidence).[5]
- The most serious risk of terminal complement blockade is life-threatening *Neisserial* infections (roughly 0.5%/year or 5% after 10 years).[3] Thus, all patients treated with eculizumab should be vaccinated against *Neisseria* with the use of locally approved vaccines.[3] In severe PNH cases, especially those with concomitant thrombosis, administration of eculizumab and vaccination can be performed on the same day. In such cases, 2 weeks of prophylactic therapy with ciprofloxacin is recommended.[6]
- The most common adverse events associated with eculizumab in the 26-week TRIUMPH[1] and 52-week SHEPHERD[2] studies in patients with PNH were headache (44%[1] and 53%[2]) and nasopharyngitis (23%[1] and 32%[2]). The majority of adverse events in both studies were mild to moderate in intensity.

Ravulizumab

- In December 2018, the US Food and Drug administration approved ravulizumab for the treatment of PNH, based on the results of two phase 3 non-inferiority clinical trials. In the first trial, ALXN1210-PNH-301, ravulizumab was administered to C5 inhibitor–naïve PNH patients and compared to eculizuamb,[7] and in the second trial, ALXN1210-PNH-302, ravulizumab and eculizumab were evaluated for noninferiority in stable PNH patients previously treated with eculizumab.[8]
- In C5 inhibitor–naïve patients, transfusion avoidance in ravulizumab (n = 125) and eculizumab (n = 121) treatment arms was achieved in 73.6% and 66.1% of patients, respectively, with a between-group difference of 6.8% (95% CI − 4.66 to +18.14; p<0.0001 for noninferiority; low-quality evidence).[7] The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of −20%.[7] The noninferiority margin for the coprimary endpoint of LDH normalization was based on a previous randomized, placebo-controlled study of eculizumab[1] and adjusted to the observed baseline LDH normalization of recent phase 1b and 2 studies, calculated with a weighted average of the proportions of LDH normalization from day 29 to day 183.[7] LDH normalization was achieved in 53.6% versus 49.4% of patients (adjusted odds ratio 1.19; 95% CI 0.80–1.77; p < 0.0001 for noninferiority; low-quality evidence).[7] The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of 0.39.[7]
- In stable patients previously treated with eculizumab, the mean percentage change in LDH in ravulizumab (n = 97) and eculizumab (n = 98) treatment arms was − 0.82% versus + 8.39% [treatment difference of 9.21% (95% CI − 0.42 to 18.84); p<0.0006 for inferiority; low-quality evidence].[8] The lower bound of the 95% CI for the difference was −0.42%, which exceeded the protocol-specified noninferiority margin of −15%, indicating that ravulizumab is noninferior to eculizumab.[8]
- A prospective, open-label, phase 3 trial evaluated the efficacy and safety of ravulizumab in adults with aHUS.[9] In this global, multicenter, single arm study, patients received intravenous ravulizumab as a weight-based loading dose on day 1, followed by weight-based maintenance doses on day 15 and every 8 weeks thereafter.[9] Low-quality evidence showed after 26 weeks of treatment with ravulizumab, complete thrombotic microangiopathy response (TMA; primary efficacy endpoint) was seen in 53.6% of complement-inhibitor naïve adult patients with aHUS (n = 56).[9]
- Common adverse effects associated with ravulizumab administration may include upper respiratory tract infection and headache.[10]
- In the United States, ravulizumab and eculizumab are available only through restricted Risk Evaluation and Mitigation Strategy (REMS) programs.[6,10] Ravulizumab and eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections.[6,10]

Monoclonal C5 Inhibitors

- There is insufficient evidence to evaluate the use of eculizumab and ravulizumab in the treatment specific subpopulations based on age, gender, ethnicity, comorbidities, disease duration or severity.

Recommendations:

- Create a new class of drugs on the PDL entitled “Biologics for Rare Diseases” and include eculizumab and ravulizumab in this new class.
- Implement clinical prior authorization criteria for eculizumab and ravulizumab to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (**Appendix 4**).
- Review costs in Executive Session.

Background:

Paroxysmal Nocturnal Hemoglobinuria

PNH is a rare disease that presents with a variety of symptoms, the most prevalent of which are hemolytic anemia, hemoglobinuria, fatigue and shortness of breath.[11] Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.[11] The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.[11] The condition is genetic, with the mutations occurring on the X-linked gene.[11] This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes.[11] Proteins responsible for the regulation of complement activity, specifically CD55 and CD59, are thereby prevented from attaching to PNH affected cells.[11] This leads to activation of C3, C5, and the terminal pathway of complement culminating in the formation of the membrane attack complex (MAC).[3] Under normal conditions, formation of the MAC is under the regulation of CD59.[3] The absence of CD59 on PNH erythrocytes leads to uncontrolled formation of the MAC resulting in complement-mediated intravascular hemolysis.[3] This chronic state of hemolysis can be exacerbated if the complement system is activated by stress due to surgery, trauma, or other triggers for inflammation.[11]

Anemia in PNH is often multifactorial and may result from a combination of hemolysis and bone marrow failure.[3] Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in lactate dehydrogenase (LDH) is common in classic PNH.[3] Patients with classic PNH often have a high percentage of PNH granulocytes (greater than 50%). PNH in the context of other primary marrow disorders usually refers to acquired aplastic anemia.[3] Thrombosis leads to severe morbidity and is the most common cause of mortality in PNH.[3] Thrombosis in PNH may occur at any site; however, venous thrombosis is more common than arterial.[3] Deep venous thrombosis, pulmonary emboli, and dermal thrombosis are also relatively common.[3] Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of intravascular hemolysis and the release of free hemoglobin.[3] Free hemoglobin is normally cleared by haptoglobin, CD163, and hemopexin.[3] These clearing mechanisms are overwhelmed in PNH and lead to accumulation of high levels of free hemoglobin in the plasma and consequently, depletion of nitric oxide.[3 3] Renal tubular damage is caused by microvascular thrombosis and accumulation of iron deposits. Raised pulmonary pressures and reduced right ventricular function caused by subclinical microthrombi and hemolysis-associated nitric oxide scavenging contribute to symptoms of fatigue and dyspnea.[3]

A classification scheme, proposed by the International PNH Interest Group, includes 3 main categories of PNH: (1) classic PNH, which includes hemolytic and thrombotic patients; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis.[12] This classification scheme has resulted in some confusion because varying degrees of bone marrow failure underlie virtually all cases of PNH; thus, the distinction between 3 categories may be difficult in some cases.[3]

PNH is rare, with occurrence estimated as high as 15.9 individuals per million worldwide.[13] Some authors indicate that this number is probably low as the disease remains undiagnosed in individuals with limited symptomatology, or with comorbid conditions that obscure the PNH diagnosis.[14] Typically most patients are diagnosed at 30 years to 40 years of age.[11] Children can be affected by PNH as well, but it is uncommon.[11] According to an analysis of 1610 patients registered in the International PNH Registry in 2012, the median age of all registered patients was 42 years, with the disease duration of 4.6 years.[15] The age range of patients in the registry was 3 to 99 years.[15] While the occurrence of PNH has no apparent ethnic or geographic distribution, there is an increased risk of thrombosis in the United States and Europe.[11] About 30 to 40% of PNH cases are reported in the United States (U.S.) and Europe, whereas less than 10% of PNH cases are reported from Asia.[11] Consequently, the incidence of thromboembolism due to PNH is higher in the U.S. and Europe compared to Japan.[16] Patients affected by PNH in the U.S. demonstrate differences in complications according to ethnic groups. African-Americans with PNH have a 73% rate of thromboembolism and Latin

Americans, about 50%.[11] White race and Asian Americans have a 36% rate of thromboembolism complications.[11] Bone marrow failure also varies with ethnicity or geography.[11] It is more common in residents of Asia, the Pacific Islands, and Latin America.[11] The reasons for these variations are not clear.[11]

In the past, PNH treatment was mostly supportive.[11] Patients were given a blood transfusion and iron supplementation for recurrent hemolysis and anemia and anti-thrombosis prophylaxis was initiated to prevent thrombosis.[11] For severe, life-threatening bone marrow complications, an allogeneic bone marrow transplant was offered.[11] The mainstay of current therapy for PNH includes drugs to block alternative complement pathways such as eculizumab or ravulizumab, and allogeneic hematopoietic stem cell transplantation.[11] There are many other anti-C5 monoclonal antibodies therapies under investigation.[11] Other novel therapy development projects are focusing on targets upstream in the complement pathway, such as C1 inhibitors, C3 inhibitors, and Factor D inhibition therapies.[11]

Atypical Hemolytic-Uremic Syndrome

Atypical HUS is a rare variant of thrombotic microangiopathy that is caused by abnormalities of the alternative complement pathway resulting in endothelial cell dysfunction and formation of microvascular thrombi that can result in serious thrombotic events such as stroke.[17] Atypical HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment.[17] Atypical HUS earned its name because it is not caused by either of the common etiological factors for typical HUS (Shiga toxin produced by *E. coli O157:H7* or *S. dysenteriae*).[17] When patients are negative for Shiga toxin, other etiologies such as genetic and sporadic causes must be further investigated.[17] The condition predominantly affects the kidneys but has the potential to cause multi-organ system dysfunction.[17] This uncommon disorder is caused by a genetic abnormality in the complement alternative pathway resulting in over-activation of the complement system and formation of microvascular thrombi.[17] Abnormalities of the complement pathway may be in the form of mutations in key complement genes or autoantibodies against specific complement factors.[17] Genetic or acquired dysregulation of the complement alternative pathway is detected in 40–60% of patients with aHUS suggesting a genetic predisposition.[17] This dysregulation is caused by mutations in genes that encode complement regulatory proteins, Factor H (FH), Factor I (FI), membrane cofactor protein, complement 3 (C3), Factor B (FB) or thrombomodulin, or presence of anti-FH antibody resulting in activation of the complement system.[17]

Complement is part of the innate immune response, helping host cells clear pathogens via three distinct pathways: classic, lectin, and alternative.[17] These pathways ultimately converge to create C3 convertase, a complex that initiates MAC (C5-9) formation to destroy target cells via attachment and lysis.[17] Over-activation of the alternative complement pathway in aHUS occurs due to either the production of FH autoantibodies or due to genetic complement protein mutations such as FH, FI, FB, C3, and thrombomodulin.[17] The complement abnormality that is associated with aHUS is very rare with only roughly 1000 reported cases.[17] The incidence of aHUS is estimated to be 0.23–0.42 cases per million; children constitute 0.10–0.11 cases per million.[17] The disease has been triggered by pregnancy, viral illness, and sepsis among other causes; approximately 30% of aHUS results from unknown mechanisms.[17] Regardless of the cause, aHUS is a rare disorder with poor clinical outcomes, and higher morbidity and mortality than infection-associated typical HUS.[17] Atypical HUS has a mortality rate of 25% and about 50% of patients may develop irreversible end stage renal disease (ESRD), requiring renal transplant or chronic dialysis.[17]

Atypical HUS can present at any age and is of acute onset in 20% of cases.[17] The clinical presentation depends upon the extent of microvascular injury and thrombosis, as well as ischemic injury to various organ systems.[17] Patients with aHUS present with hemolytic anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets <150,000/mm^3), and impaired renal function. Renal impairment is frequent; most common manifestations are proteinuria, hematuria, hypertension, and azotemia.[17] While proteinuria is typically mild, nephrotic range proteinuria may occur.[17] A majority of patients require chronic renal replacement therapy.[17] Hypertension is often moderate to severe, due to vascular disease and volume expansion.[17] Atypical HUS presents as a systemic disease, and extra-renal features are seen in 20% and a catastrophic presentation with multi-organ involvement in 5% of patients.[17]

Therapy of aHUS is supportive, with attention to management of acute kidney injury and systemic complications.[17] The use of packed red blood cells is necessary in patients with severe anemia. Platelet transfusions are rarely required, except in counts less than 10,000/mm^3, or thrombocytopenia associated with active bleeding or in patients undergoing invasive procedures.[17] Fluid and electrolyte management is important to maintain intravascular volume status and combat the consequences of acute kidney injury and multisystem organ failure.[17] Electrolyte disturbances should be promptly corrected and nephrotoxic medications avoided.[17] Hypertension should be managed with appropriate agents.[17] Renal replacement therapy is required in patients with uremia, fluid overload, or electrolyte abnormalities.[17] No adequate, well-controlled trials have been conducted to establish the efficacy of plasma therapy in aHUS.[17] By preventing MAC formation, eculizumab and ravulizumab inhibit the mechanism by which aHUS causes pathology, making these novel drugs promising treatments for aHUS patients.[17]

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease in which antibodies bind to acetylcholine receptors or functionally related molecules in the postsynaptic membrane at the neuromuscular junction.[18] Autoantibodies may be produced against 1) the skeletal muscle acetylcholine receptor (AChR); 2) muscle-specific kinase, a receptor tyrosine kinase critical for the maintenance of neuromuscular synapses; 3) low-density lipoprotein receptor-related protein 4, an important molecular binding partner for muscle-specific kinase; and 4) other muscle endplate proteins.[19] The antibodies induce weakness of skeletal muscles, which result in impaired speech, difficulty swallowing or chewing, shortness of breath, drooping of one or both eyelids, blurred vision and weakness in limbs.[18] In the most common type of MG, autoantibodies are produced that target the skeletal muscle AChR, reducing the number of functional AChRs, and causing morphological damage to the endplate membrane, resulting in the clinical phenotype of fatigable muscle weakness.[19] In AchR antibody-positive MG, the production of autoantibodies by pathogenic B cells is T cell-dependent.[19] Although anti-AChR antibodies directly contribute to the degradation of AChR at the neuromuscular junction, autoreactive T cells provide help to B cells that synthesize anti-AChR antibodies.[19] The situation with AChR-associated MG becomes more complicated as there are clinical and immunological differences in patients with thymic abnormalities (thymic hyperplasia vs thymoma) versus no thymic pathology.[19] Approximately 70% of patients with MG with anti-AChR antibodies have thymic follicular hyperplasia, approximately 10% have thymomas, and the remainder have a histologically normal or atrophic thymus gland.[19] The alterations of the immune system that occur with thymic hyperplasia versus thymoma are quite distinct.[19] In patients with thymic hyperplasia, there is evidence that the thymus is the primary site of immune sensitization to the AChR and may play a role in perpetuating the disease.[19] Thymic follicular hyperplasia usually occurs in early-onset MG and is characterized by the development of lymphoid germinal centers (GCs) containing a large number of B cells.[19] The formation of these ectopic GCs may be triggered by a viral infection or other source of inflammation, but this has not been clearly demonstrated.[19]

Myasthenia gravis is the most common disorder of the neuromuscular junction, with an estimated prevalence of 14 to 20 per 100,000 people, approximately 36,000 to 60,000 cases in the United States.[20] Myasthenia gravis occurs at any age, but there tends to be a bimodal distribution to the age of onset, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).[20] It characteristically presents with fatigable weakness, often initially involving the ocular muscles and manifesting as intermittent ptosis and diplopia.[21] Ultimately, the disease generalizes throughout the body in two-thirds of patients, leading to weakness of bulbar, neck, limb, and respiratory muscles.[21]

The majority of patients with generalized MG, and roughly half of patients with purely ocular disease, harbor antibodies to skeletal muscle AChRs.[21] Patients with refractory generalized MG, representing approximately 10–15% of all patients with MG, do not respond to long-term treatment with corticosteroids or multiple immunosuppressant therapies (ISTs), or they have intolerable side-effects to these therapies or require ongoing treatment with either intravenous immunoglobulin or plasma exchange.[4] This heterogeneous patient population continues to have disease symptoms and persistent morbidities, despite substantial use of ISTs, including difficulties with speech, swallowing, and mobility, impairment of respiratory function, and extreme fatigue, with substantial

negative effects on activities of daily living and quality of life.[4] Patients with refractory generalized MG might also have frequent exacerbations, which can be life-threatening and require admission to hospital or intensive care, and cause episodes of respiratory failure that require mechanical ventilation.[4] The Myasthenia Gravis Foundation of America (MGFA) has developed a classification of MG depending on disease severity ranging from Class I (least severe) to Class V (most severe).[22] Class I disease is defined by the MGFA as any ocular weakness but no other symptoms.[22] Class V patients have worsening myasthenic weakness that requires intubation or noninvasive ventilation to avoid intubation.[22]

The myasthenia gravis activities of daily living (MG-ADL) is a patient-reported, physician administered scoring tool.[23] Eight domains (talking, chewing, swallowing, breathing, ability to brush teeth, ability to arise from chair, vision and eyelid droop) are scored on a scale of 0 (normal) to 3 (severe).[23] A total score of 24 is possible; higher scores indicate more disability.[4] A 2-point reduction in the MG-ADL is considered clinical meaningful improvement.[23] The Quantitative Myasthenia Gravis (QMG) score is a validated 13-item disease-severity physician-reported assessment tool.[24] This tool evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item).[24] The scores are not weighted, but each item is graded on a scale of 0 (no weakness) to 3 (severe weakness).[24] Total scores range from 0 to 39, higher scores represent greater disease burden.[24] A 3-point reduction in QMG total score considered a clinically meaningful improvement.[25]

As an immune-mediated disorder, MG can respond to several ISTs, such as corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus and cyclosporine.[22] There is widespread variation in practice with respect to choice of IS agent since there is little literature comparing them.[22] Expert consensus from MGFA 2013 guidance support the use of azathioprine as a first-line immunosuppressive agent in MG based on sparse randomized clinical trial (RCT) evidence.[22] Evidence from RCTs supports the use of cyclosporine in MG, but potential serious adverse effects and drug interactions limit its use.[22] Although available RCT evidence does not support the use of mycophenolate and tacrolimus in MG, both are widely used, and one or both are recommended in several national MG treatment guidelines.[22]

In October 2019, the MGFA appointed a Task Force to update treatment guidance for MG, and a panel of 15 international experts was convened.[26] The previous recommendations for thymectomy were updated. Recommendations for the use of methotrexate, rituximab and eculizumab were re-evaluated based on available evidence.[26] Although robust evidence from RCTs is insufficient, oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents.[26] Rituximab should be considered as an early therapeutic option in patients with AchR antibody-positive generalized MG who have an unsatisfactory response to initial immunotherapy.[26] Eculizumab should be considered in the treatment of severe, refractory, AchR antibody-positive generalized MG.[26] The role of eculizumab in the treatment of MG is likely to evolve over time.[26] Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals.[26]

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.

NEW DRUG EVALUATION: Eculizumab

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.

Eculizumab is a humanized monoclonal antibody that blocks terminal complement by binding to C5. Eculizumab prevents C5 conversion into C5a and C5b factors; thus, effectively inhibiting MAC formation and complement-mediated lysis.[11] FDA-approved indications for eculizumab include:

- Treatment of PNH to reduce hemolysis: approved March 2007
- Treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy: approved September 2011
- Treatment of MG in adult patients who are anti-acetylcholine receptor antibody positive: approved October 2017
- Treatment of NMOSD in adult patients who are anti-AQP4 antibody-positive: approved June 2019 (addressed in a separate class update presented to the P & T Committee, April 2021)

Clinical Efficacy:

Paroxysmal Nocturnal Hemoglobinuria

The efficacy and safety of eculizumab in adults with PNH was demonstrated in 2 multinational, phase 3 trials. In the double-blind TRIUMPH trial, patients with severe PNH disease were randomized to eculizumab or placebo and evaluated over 26 weeks (n=87).[1] The open-label, single-arm, 52 week SHEPHERD trial evaluated eculizumab in a broader PNH patient population (e.g., patients with thrombocytopenia and mild anemia; n=97).[2] The eculizumab intravenous regimen administered in both studies was an induction dosage of 600 mg every week for 4 weeks, then 900 mg at week 5 followed by a maintenance dosage of 900 mg every 2 weeks.[1,2]

The TRIUMPH study consisted of a 2-week screening period, an observation period of up to 3 months, and a 26-week treatment period.[1] Patients 18 years of age or older who had received at least four transfusions during the previous 12 months were eligible.[1] Patients who did not require a transfusion during the observation period were considered ineligible for study participation.[1] During the observation period a transfusion administered to a patient who had a hemoglobin level of 9 g per deciliter or less with symptoms or 7 g per deciliter or less with or without symptoms qualified the patient for the study and established the individual patient's hemoglobin set point. This set point would define each patient's hemoglobin stabilization and transfusion outcomes.[1] PNH type III erythrocyte proportion of 10% or more, platelet counts of at least 100,000/mm^3, and lactate dehydrogenase (LDH) levels that were at least 1.5 times the upper limit of the normal range were also required.[1] Concomitant administration of erythropoietin, immunosuppressive drugs, corticosteroids, coumarins, low-molecular-weight heparins, iron supplements, and folic acid were permitted, provided that the doses were constant before and throughout the study.[1] Because persons who have a genetic deficiency of terminal complement proteins have an increased risk of meningococcal infections, all patients were vaccinated against *Neisseria meningitidis* with locally approved vaccines.[1]

The co-primary endpoints in the TRIUMPH trial were the stabilization of hemoglobin levels and the number of units of packed red cells transfused.[1] Patients received transfusions when they had symptoms resulting from anemia and their hemoglobin levels reached the individualized, predetermined set point.[1] Prespecified secondary end points included transfusion independence; hemolysis, as measured by the LDH value for the area under the curve from baseline to

26 weeks; and changes in the level of fatigue, as assessed from baseline to 26 weeks with the use of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[1] The FACIT-Fatigue scores can range from 0 to 52, with higher scores indicating improvement in fatigue.[1] The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) was used to assess quality of life. EORTC QLQ-C30 scores can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and single item measures indicating improvement.[1]

Stabilization of hemoglobin levels and the requirement for packed red cell transfusions were improved significantly more with eculizumab than with placebo after 26 weeks of treatment.[1] Forty-nine percent of all patients in the eculizumab group were transfusion independent compared with 0% of patients in the placebo group ($p < 0.001$).[1] Hemolysis was also significantly reduced with eculizumab compared with placebo, as determined by lower mean levels of LDH in the eculizumab treatment group.[1] The median area under the concentration-time curve (AUC) for LDH was 86% lower with eculizumab than with placebo (58,587 vs. 411,822 U/L per day respectively; $p < 0.001$).[1] Mean hemoglobin levels increased from 10.0 to 10.1 g/dL in the eculizumab group and decreased from 9.7 to 8.9 g/dL in the placebo group ($p < 0.001$ eculizumab vs placebo).[1] Reticulocyte counts did not change significantly from baseline and remained elevated at week 26 in both groups.[1]

Consistent with improvements in other outcomes, by week 26, Health-Related Quality Of Life (HR-QOL) had improved significantly more in the eculizumab group than in the placebo group, as determined by the EORTC-QLQ-C30 and FACIT-Fatigue instruments ($p < 0.001$ for both).[1] The EORTC-QLQ-C30 instrument demonstrated significant improvements in all five functioning scales and two of three symptom scales (fatigue [$p < 0.001$], pain [$p=0.002$] and nausea and vomiting [$p=0.06$]).[1] Improvements in the single-item measures of dyspnea, loss of appetite and insomnia were also significantly ($p<0.01$) greater in the eculizumab group than in the placebo group, whereas changes in financial difficulties, constipation and diarrhea were not significant between groups.[1] Patients in the eculizumab group had a mean increase (improvement) in scores on the FACIT-Fatigue instrument of 6.4 ± 1.2 points from baseline to week 26, whereas in the placebo group the mean score change of -4.0 ± 1.7 points during this period, for a total difference between the two groups of 10.4 points.[1]

In the open-label, single-arm SHEPHERD trial, the primary efficacy end point was hemolysis as assessed by LDH area under the curve (AUC).[2] All patients were vaccinated against *Neisseria meningitidis* at least 14 days prior to receiving the first dose of eculizumab.[2] Throughout the 52-week study, patients received transfusions with packed red blood cells if medically indicated.[2] The secondary efficacy end points included fatigue as measured by the FACIT-Fatigue instrument and LDH change from baseline.[2] The primary safety end points were adverse events, clinical laboratories, electrocardiogram (ECG) data, and vital signs.[2] The SHEPHERD study was designed to evaluate the safety and efficacy of eculizumab in PNH patients by relaxing the inclusion criteria of TRIUMPH study, to allow patients with minimal transfusion support and evidence of thrombocytopenia to participate.[2] PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter were eligible for study enrollment.[2] Baseline transfusion requirements and platelet counts were statistically different between SHEPHERD and TRIUMPH ($p < 0.001$ and $p = 0.009$, respectively).[2]

In the SHEPHERD trial, hemolysis was significantly improved from baseline with eculizumab treatment, as demonstrated by the reduction in LDH AUC (median change -632,264 IU/L per day; $p<0.001$) after 52 weeks of treatment.[2] Mean LDH was significantly reduced by 87%, from 2201 IU/L at baseline to 297 IU/L (normal range is 80-225 U/L) at week 52 ($p<0.001$).[2] Eculizumab significantly reduced requirements for PRBC transfusions throughout the study.[2] During 52 weeks of eculizumab therapy, the median number of units transfused per patient was 0 compared with 8 units in the year prior to treatment ($p<0.001$).[2] The mean number of transfusions per patient was reduced from 12.3 to 5.9 units, a decrease of 52%.[2] Forty-nine (51%) patients were transfusion independent throughout 52 weeks of eculizumab therapy ($p<0.001$).[2] At week 52, the FACIT-Fatigue score had improved by 12.2 points ($p<0.001$) from baseline values.[2] Similarly, eculizumab significantly improved HR-QOL, as determined by the EORTC QLQ-C30 instrument, with global health status ($p<0.001$), all five scales for

functioning (p<0.001), all three symptom scales (p<0.002) and four of six single-item measures (p<0.001) compared with baseline.[2] More details for these trials are included in **Table 5.**

Trial Limitations

The TRIUMPH trial was randomized, double-blinded and placebo-controlled in patients that had severe PNH. In contrast, the SHEPHERD trial was conducted in a broader range of PNH patients, but was single-armed, non-randomized, and open-label which introduced a higher risk of bias. Both trials were relatively short-term considering PNH is a chronic condition. Finally, both trials were designed, conducted and funded by the manufacturer.

Myasthenia Gravis

The randomized, placebo-controlled, double-blind, multicenter, phase 3 REGAIN study evaluated the safety and efficacy of eculizumab in 125 adults with IST refractory, AchR antibody-positive, generalized MG.[4] Eculizumab was administered in a dosing regimen evaluated in a phase 2 trial of MG patients: 900 mg every week for 4 weeks, 1200 mg at week, then 1200 mg every 2 weeks. The REGAIN study included patients aged ≥ 18 years with MG, a positive serological test for anti-AChR antibodies, impaired activities of daily living (i.e. MG-ADL score of 6 or greater) and MGFA class II–IV disease.[4] Patients were also required to have received 2 or more ISTs for 12 months without symptom control or 1 or more ISTs with chronic intravenous immunoglobulin or plasma exchange therapy (PLEX), without symptom control over 12 months.[4] Patients were randomized to eculizumab or placebo for 26 weeks.[4] Those receiving prior therapy with a cholinesterase inhibitor, oral corticosteroid or other ISTs were to continue treatment at the same dose and schedule throughout the study, unless an adjustment was needed due to a compelling medical reason.[4] Owing to the severity of disease, rescue medication (e.g. high-dose corticosteroids, intravenous immunoglobulin, plasma exchange therapy) was permitted at the physician's discretion.[4] All randomized patients were required to have been vaccinated against *Neisseria meningitides* with locally approved vaccines.[4]

The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score.[4] Prespecified worst-rank ANCOVA of each patient was ranked from 1 (best) to 125 (worst), whereby the patient who had a myasthenia gravis crisis was ranked lowest and patients who received rescue therapy or dropped out of the study were ranked lowest according to time to event; all other patients were ranked higher according to change from baseline to week 26 or last observation carried forward (LOCF).[4] For the prespecified outcome change from baseline in worst-rank ANCOVA, 103 patients were ranked by the change from baseline (rank 1–103), 103 completed 26 weeks without rescue therapy, 22 were in the lowest-rank group, ranked by time to event (rank 104–125), one had a myasthenia gravis crisis and rescue therapy (rank 125), 17 other patients required rescue therapy by study end, and four discontinued for any reason.[4] The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank 56.6 vs. 68.3; rank-based treatment difference −11.7; 95% CI −24.3 to 0.96; p=0.0698).[4]

A key secondary endpoint in REGAIN trial was the change from baseline in the QMG total score at Week 26. A statistically significant difference favoring eculizumab was observed in the mean change from baseline to Week 26 in QMG total scores (-4.6 points in the eculizumab-treated group compared with -1.6 points in the placebo-treated group; P=0.001).[4] In a sensitivity analyses, patients receiving eculizumab showed an initial improvement in MG-ADL total score by week 1, and QMG total score by week 2, with most of the treatment effect occurring by week 12 and sustained to week 26.[4] Change in MG-ADL (standard error of the mean) in eculizumab-treated patients was -4.2 compared with -2.3 in placebo-treated patients (Difference: -1.9; 95% CI -3.3 to -0.06; P=0.006).[4] The mean change from baseline at week 26 in MG-ADL and QMG score was greater with eculizumab than with placebo based on repeated-measures analyses with and without immunosuppressive therapies as a covariate.[4] The use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result; further research into the role of complement is needed.[4] More

details for this trial are included in **Table 5.** Based on the results of this trial, the MGFA recommends eculizumab should be considered in generalized MG patients with severe disease refractory to 2 or more ISTs or dependence on maintenance intravenous immunoglobulin or PLEX.[26]

Atypical Hemolytic-Uremic Syndrome

Eculizumab received FDA approval as an orphan drug via the FDA's accelerated approval pathway in 2011. The dosing regimen for eculizumab in aHUS consists of four, weekly 900 mg IV induction doses and then the patient is transitioned to maintenance dosing at 1200 mg IV every two weeks.[6] Two single-arm, multi-center, 26-week, phase 2 trials evaluated intravenous eculizumab inhibited complement-mediated thrombotic microangiopathy (TMA) in patients aged 12 years and older with aHUS.[5] Complete TMA response was defined as: hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine in two consecutive measurements for four or more weeks).[5] Trial C08-002 included patients with progressive TMA who were refractory to plasma exchange (n=17; 16 adults and 1 adolescent) while trial C08–003 included patients with chronic dependence on plasma exchange defined as no more than a 25% decrease in platelet counts during plasma exchange in the 8 weeks prior (n=20; 15 adults and 5 adolescents). At least 80% of patients achieved TMA-free status in both trials.[5] In addition, time-dependent improvements in renal function were observed.[5] At week 26, 65% and 25% of patients demonstrated complete TMA response in both trials.[5] At 26 weeks, the platelet count was significantly increased in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, and thrombotic microangiopathic event-free status was achieved in 80% of patients with a long disease duration and chronic kidney disease who received long-term plasma exchange.[5] Renal function also improved with eculizumab therapy in both studies.[5]

Due to the high risk of bias (single-arm, open label, non-randomized, small sample size) in both of these trials, they are not presented in **Table 5** (Comparative Evidence Table).

Limitation of Use: Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).[6]

Clinical Safety:

The most serious risk of terminal complement blockade is life-threatening meningococcal *infections* (roughly 0.5%/year or 5% after 10 years).[3] Thus, all patients treated with eculizumab should be vaccinated against *N. meningitidis* with the use of locally approved vaccines.[3] In severe PNH cases, especially those with concomitant thrombosis, administration of eculizumab and vaccination can be performed on the same day. In such cases, 2 weeks of prophylactic therapy with ciprofloxacin is recommended. In the United States eculizumab is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.[6]

The most common adverse events associated with eculizumab in the 26-week TRIUMPH[1] and 52-week SHEPHERD[2] studies in patients with PNH were headache (44%[1] and 53%[2]) and nasopharyngitis (23%[1] and 32%[2]). The majority of adverse events in both studies were mild to moderate in intensity.[1] More details about adverse events reported in the TRIUMPH trial compared to placebo are presented in **Table 1**.

In the REGAIN trial the most common adverse events in both groups were headache and upper respiratory tract infection (experienced by 10 patients [16%] for both events in the eculizumab group and 12 [19%] for both in the placebo group).[4] Myasthenia gravis exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group.[4] Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy.[4] More details about adverse events reported in the REGAIN trial are presented in **Table 2**. Adverse effects reported in patients with aHUS are outlined in **Table 3.**

Table 1. Adverse Reactions Reported in 10% or More of Eculizumab-Treated Patients with PNH and Greater than Placebo-Treated Patients[6]

Reaction	Eculizumab (n=43)	Placebo (n=44)
Headache	19 (44%)	12 (27%)
Nasopharyngitis	10 (23%)	8 (18%)
Back Pain	8 (19%)	4 (9%)
Nausea	7 (16%)	5 (11%)
Fatigue	5 (12%)	1 (2%)
Cough	5 (12%)	4 (9%)

Table 2. Adverse Reactions Reported in 5% or More of Eculizumab-Treated Patients with MH and Greater than Placebo-Treated Patients[6]

Reaction	Eculizumab (n=62)	Placebo (n=63)
Musculoskeletal Pain	9 (15%)	5 (8%)
Abdominal Pain	5 (8%)	3 (5%)
Peripheral Edema	5 (8%)	3 (5%)
Herpes Simplex Infections	5 (8%)	1 (2%)
Contusion	5 (8%)	2 (3%)
Pyrexia	4 (7%)	2 (3%)

Table 3. Adverse Reactions Reported in 10% or More of Eculizumab-Treated Adults and Adolescents with aHUS [6]

Reaction	Eculizumab (n=78)
Headache	32 (41%)
Hypertension	26 (33%)
Nasopharyngitis	21 (27%)
Nausea	18 (23%)
Cough	18 (23%)
Fatigue	10 (13%)
Back Pain	8 (10%)

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Stabilize platelet count (aHUS)
2) Stabilize LDH count (aHUS)
3) Improve fatigue (PNH)
3) Improved functional status (PNH, aHUS, MG)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduced need for transfusions (PNH)
2) Stabilized hemoglobin level (PNH)
3) Improved MG-ADL score (MG)

Table 4. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Complement protein C5 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 5 L to 8 L; Protein Binding N/R
Elimination	aHUS: 14.6 mL/hour; PNH: 22 mL/hour
Half-Life	Ranges from 270 hours to 414 hours - aHUS: 291 hours; PNH: 272 hours
Metabolism	N/R

Abbreviations: aHUS = atypical hemolytic-uremic syndrome; kg = kilogram; mL = milliliters; L=liters; N/A=not applicable; N/R=not reported; PNH = paroxysmal nocturnal hemoglobinuria

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. Hillmen et al.[1] TRIUMPH DB, PC, MC, phase 3 RCT	1. Eculizumab 600 mg IV once a week x 4 weeks, followed by 900 mg 1 week later and then 900 mg every other week through week 26 2. Placebo	Demographics: 1.Male: 40% 2.Median age: 39 yo 3.Mean Hgb: 8 g/dL 4.Use of steroids: 34% Key Inclusion Criteria: 1.Adults ≥18 yo who had received at least 4 transfusions in the previous 12 mos 2.PNH type 3 erythrocyte > 10% 3.Platelet count > 100,000/microliter 4. LDH > 1.5 ULN Key Exclusion Criteria: 1.Reciept of transfusions during the 12 mos prior to study entry with a pre-transfusion mean hemoglobin > 10.5 g/dL 3. Complement deficiency 4.History of meningococcal disease 5.History of bone marrow transplant	ITT: 1. 43 2. 44 PP: 1. 41 2. 34 Attrition: 1. 2 (5%) 2. 10 (23%)	Co-Primary Endpoints: A. Number of patients with stabilization of hemoglobin levels in the absence of transfusions 1. 21 (49%) 2. 0 (0%) P<0.001 B. Median number of units of PRBC transfused per patient over 26 weeks 1. 0 units 2. 10 units P<0.001 Secondary Endpoints: A. Median LDL AUC level over 26 weeks 1. 58,587 U/L 2. 411,822 U/L Difference: 86% P<0.001 B. Change in FACIT-Fatigue score 1. +6.4 ± 1.2 points 2. – 4.0 ± 1.7 points Difference: +10.4 points P<0.001	49/2 NA NA NA	Serious Adverse Effects 1. 4 (9%) 2. 9 (21%) Headache 1. 19 (44%) 2. 12 (27%) Nasopharyngitis 1. 10 (23%) 2. 8 (18%) Upper Respiratory Tract Infection 1. 6 (14%) 2. 10 (23%) p-value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via central IVRS. Stratified according to number of units of PRBC transfused in the previous 12 mos. Baseline characteristics were balanced between groups. Performance Bias: Low. Double-blind study design: participants and investigators were masked to treatment assignment. Protocol does not describe if eculizumab and placebo were similar in appearance. Detection Bias: Unclear. Protocol does not describe if eculizumab and placebo were similar in appearance. Attrition Bias: High. More patients in the placebo arm withdrew due to perceived lack of efficacy. Reporting Bias: Unclear. Protocol unavailable online. Other Bias: Unclear. Funded by Alexion Pharmaceuticals. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol. **Applicability**: Patient: Strict inclusion criteria limited enrollment to patients with severe PNH. Intervention: Dosing evaluated in phase 2 open label trial. Comparator: No other approved treatments available; placebo comparator is appropriate. Outcomes: Reduction in transfusion frequency is appropriate endpoint for PNH. Setting: 34 sites in the United States, Canada, Europe, and Australia

2.Brodsky, et al.[2] SHEPHERD OL, phase 3 study	1. Eculizumab 600 mg IV once a week x 4 weeks, followed by 900 mg 1 week later and then 900 mg every other week through week 52	Demographics: 1.Male: 50% 2.Median age: 41 yo 3. Race-White: 91% 4. Median PNH duration: 4.9 yrs 5. Baseline platelet count range: 23-355/microliter 6.Basline LDH range: 537-5245 U/L Key Inclusion Criteria: 1.Adults > 18 yo who had received at least 1 transfusion in the previous 24 mos 2.PNH type 3 erythrocyte > 10% 3.Platelet count > 30,000/microliter 4. LDH > 1.5 ULN Key Exclusion Criteria: 1. Complement deficiency 2.History of meningococcal disease 3.History of bone marrow transplant	ITT: 1. 97 PP: 1. 96 Attrition: 1. 1 (1%)	Primary Endpoint: Median reduction in LDH AUC over 52 weeks compared to baseline 1. -632,264 U/L/day P<0.001 Secondary Endpoints: A. Mean LDH level (normal range: 103 to 223 U/L) 1. Baseline: 2,201 ± 105 U/L 2. 52 weeks: 297 ± 21 U/L P<0.001 B. Mean Change in FACIT-Fatigue score from baseline to 52 weeks 1.+12.2 ± 1.1 P<0.001	NA NA NA	Headache 1. 51 (53%) Nasopharyngitis 1. 31 (32%) Upper Respiratory Tract Infection 1. 29 (30%)		**Risk of Bias (low/high/unclear)**: Selection Bias: High. Open-label, single armed study. Performance Bias: High. Open-label design. Detection Bias: High. Single-arm study. Attrition Bias: Low. 1 patient withdrew due to adverse effect unrelated to study drug. Reporting Bias: Low. Protocol available at clinicaltrials.gov Other Bias: High. Trial funded by Alexion Pharmaceuticals. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol. **Applicability**: Patient: Inclusion criteria allowed minimal transfusion requirements or evidence of thrombocytopenia, allowing for broader enrollment of adults with PNH. Intervention: Dosing evaluated in phase 2 open label trial. Comparator: Single arm trial: no comparator evaluated. Outcomes: Safety over 52 week and efficacy as assessed by change in LDH. Setting: Several centers in the U.S.

3. Howard, JF et al.[4] REGAIN DB, PG, PC, MC phase 3 RCT over 26 weeks	1. Eculizumab 900 mg IV once a week x 4 weeks, followed by 1200 mg 1 week later and then 1200 mg every other week through week 26 2. Matched placebo	Demographics: 1.Female Gender: 66% 2.Race: White: 76% Asian: 15% 2.Duration of MG: 8.2 years 3. Age: 47 yo 4.MG-ADL score: 10.2 5.MGFA disease classification IIa or IIIa: 50% IIb or IIIb: 41% Key Inclusion Criteria: 1.Adults aged 18 yo and older with MG and positive anti-AchR antibodies 2.MG Clinical Classification: II-IV 3. MG-ADL score ≥ 6 4.Failed IST treatment Key Exclusion Criteria: 1.History of thymoma or other neoplasm of the thymus 2. Thyectomy less than 12 mos prior to study 3.Use of IVIG or plasma exchange less than 4 weeks prior to study 4. Use of rituximab less than 6 mos prior to screening	ITT: 1. 62 2. 63 PP: 1. 57 2. 61 Attrition: 1. 5 (8%) 2. 3 (5%)	Primary Endpoint: Mean-ranked change in MG-ADL score from baseline to week 26 (least-squares mean rank) 1. 56.6 2. 68.3 Difference: -11.7 95% CI -24.3 to 0.96 P=0.0698 Secondary Endpoints A. Change in MG-ADL (standard error of the mean) 1.-4.2 2.-2.3 Difference: -1.9 95% CI -3.3 to -0.06 P=0.006 B. Change from baseline in the QMG total score at Week 26 (least-squares mean) 1.-4.6 2.-1.6 Difference -3.0 95% CI -4.6 to -1.3 P=0.001	NS NA NA	Serious Adverse Events 1. 9 (15%) 2. 18 (29%) Headache 1. 10 (16%) 2. 12 (19%) Upper Respiratory Infection: 1. 10(16%) 2. 12 (19%) 95% CI and p-value NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 1:1 to eculizumab or placebo via IVRS system. Patients stratified according to disease severity. Treatment groups were generally well matched regarding demographic characteristics, disease status, and medical history. Performance Bias: Low. Patients, investigators, staff, and outcome assessors were masked to treatment assignment. Detection Bias: Low. Placebo was matched to eculizumab. Attrition Bias: Low. Attrition rates were low in both arms. Reporting Bias: Low. Protocol available on-line. Outcomes reported as pre-specified. Other Bias: High. Trial funded by Alexion Pharmaceuticals. The funder of the study had a role in study design, study conduct, and data collection. The funding source was responsible for the statistical analysis plan and protocol as well as the final clinical study report. In addition, the medical writer was an employee of the funding source and additional employees provided a review of the manuscript. **Applicability**: Patient: Representative of MG population who had failed prior IST. Intervention: Dosing evaluated in phase 2 trial. Comparator: Placebo is an appropriate comparator. Outcomes: Quality of life is a reasonable outcome to evaluate therapy using the validated MG-ADL. Secondary outcomes were focused on safety endpoints. Setting: 76 hospitals and specialized clinics in 17 countries across North America, Latin America, Europe, and Asia

Abbreviations [alphabetical order]: AchR = Acetylcholine Receptor; ARR = absolute risk reduction; AUC = Area Under the Curve; CI = confidence interval; DB = double blind; dL = deciliter; FACIT-F Score = Functional Assessment of Chronic Illness Therapy-Fatigue; IST = Immunosuppressive Therapy; ITT = intention to treat; IVIg = Intravenous Immunoglobulin; IVRS = interactive voice-response system; LDH = lactate dehydrogenase; MC = Multi-Center; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG = Myasthenia Gravis; MGFA = Myasthenia Gravis Foundation of America; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PG = Parallel Group; PC = Placebo-Controlled; PNH = Paroxysmal Nocturnal Hemoglobinuria; PP = per protocol; PRBC = packed red blood cells; QMG = Quantitative Myasthenia Gravis ; RCT= Randomized Controlled Trial; ULN = upper limit normal; U = unit; yo = years old

NEW DRUG EVALUATION: Ravulizumab

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:

Ravulizumab (Ultomiris™), a humanized monoclonal antibody, is a complement C5 inhibitor FDA-approved for the treatment of PNH and aHUS. In December 2018, the US Food and Drug administration approved ravulizumab for the treatment of PNH. Efficacy data for the use of ravulizumab in adults with PNH are described and evaluated below in **Table 9.** Treatment of adults and pediatric patients one month of age and older with aHUS to inhibit complement-mediated thrombotic microangiopathy (TMA) received FDA approval October 2020.[10]

Like eculizumab, the first-generation C5 inhibitor, ravulizumab binds specifically and with high affinity to the complement protein C5, thereby preventing formation of the terminal complement complex C5b-9, which mediates cell lysis.[27] The drug was developed by re-engineering eculizumab to create a novel longer-acting antibody, requiring less frequent infusions than eculizumab.[27] Ravulizumab has a 3 to 4 times longer half-life compared to eculizumab and requires dosing every eight weeks.[27] In adults with PNH and aHUS, ravulizumab is administered via intravenous infusion according to weight, commencing with a loading dose and followed 2 weeks later with a maintenance dose, which is continued once every 8 weeks.[10] For patients switching from eculizumab to ravulizumab, a loading dose should be administered 2 weeks after the last eculizumab infusion, followed by a maintenance dose 2 weeks later, then once every 8 weeks.[10]

Paroxysmal Nocturnal Hemoglobinuria

FDA approval for the use of ravulizumab in the treatment of PNH was based on the results of two phase 3 clinical trials. In the first trial, ALXN1210-PNH-301, ravulizumab was administered to C5 inhibitor–naïve PNH patients,[7] and in the second trial, ALXN1210-PNH-302,[8] stable PNH patients previously treated with eculizumab were enrolled in the study. Patients in both studies had been vaccinated against meningococcal infections at least 3 years prior to treatment. In both multi-center, randomized, open-label, phase 3 noninferiority trials, ravulizumab treatment was initiated with a loading dose on day 1, followed by maintenance doses on day 15 and every 8 weeks thereafter; all doses were based on weight.[7] The intravenous ravulizumab group received a loading dose (2400 mg for patients weighing ≥40 to <60 kg, 2700 mg for patients ≥60 kg to <100 kg, and 3000 mg for patients ≥100 kg) on day 1, followed by maintenance doses of ravulizumab (3000 mg for patients ≥40 to <60 kg, 3300 mg for patients ≥60 to <100 kg, and 3600 mg for patients ≥100 kg) on day 15 and every 8 weeks thereafter.[7] Patients assigned to eculizumab received induction doses of 600 mg on days 1, 8, 15, and 22 only in the 301 trial, followed by maintenance dosing of 900 mg on day 29 and every 2 weeks thereafter per the approved PNH dosing regimen.[7]

In the trial in C5 inhibitor–naïve patients, those with LDH levels ≥ 1.5 times the upper limit of normal (ULN) and at least one PNH symptom were eligible for inclusion. Co-primary efficacy end points were proportion of patients remaining transfusion-free and LDH normalization.[7] Secondary end points were percent

change from baseline in LDH, change from baseline in FACIT–Fatigue score, proportion of patients with breakthrough hemolysis, and stabilized hemoglobin levels.[7] The study consisted of a 4-week screening period and a 26-week randomized treatment period to evaluate the efficacy and safety of ravulizumab versus eculizumab, followed by an extension period of up to 2 years, during which all patients receive ravulizumab.[7] Patients were stratified into 6 groups based on transfusion history (0, 1-14, or >14 units of packed red blood cells in the 1 year before the first dose of study drug) and LDH screening level (1.5 to <3 times the ULN or ≥3× ULN).[7] Enrollment of patients without a history of transfusion in the past year was capped at 20%. Hemoglobin levels were evaluated before randomization and within 5 days before study drug initiation; patients were transfused, if necessary, to reach the protocol-specified hemoglobin level.[7]

In C5 inhibitor–naïve patients, transfusion avoidance in ravulizumab (n = 125) and eculizumab (n = 121) treatment arms was achieved in 73.6% versus 66.1% of patients, respectively, with a between-group difference of 6.8% (95% CI − 4.66 to +18.14; p<0.0001 for noninferiority).[7] The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of −20%.[7] The noninferiority margin for the coprimary endpoint of LDH normalization was based on a previous randomized, placebo-controlled study of eculizumab[1] and adjusted to the observed baseline LDH normalization of recent phase 1b and 2 studies, calculated with a weighted average of the proportions of LDH normalization from day 29 to day 183.[7] LDH normalization was achieved in 53.6% versus 49.4% of patients (adjusted odds ratio 1.19; 95% CI 0.80–1.77; p < 0.0001 for noninferiority).[7] The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of 0.39.[7] Ravulizumab was also noninferior to eculizumab in all key secondary endpoints: percent reduction in LDH (−76.8% vs. −76.0%; difference -0.83%; 95% CI, −5.21 to 3.56), change in FACIT-Fatigue score (7.07 vs. 6.40; difference 0.67; 95% CI, −1.21 to 2.55), breakthrough hemolysis (4.0% vs. 10.7%; difference −6.7%; 95% CI −14.21 to 0.18), and stabilized hemoglobin (68.0% vs. 64.5%; difference 2.9%; 95% CI −8.80 to 14.64) .[7]

The eculizumab pretreatment trial recruited stable patients who had received eculizumab for 6 months or more before study entry, with LDH levels of ≤ 1.5 × ULN at screening.[8] In this phase 3, open-label, noninferiority, multicenter study, 195 PNH patients on labeled-dose (900 mg every 2 weeks) eculizumab for greater than 6 months were randomly assigned 1:1 to switch to ravulizumab (n = 97) or continue eculizumab (n = 98).[8] The study consisted of a 4-week screening period followed by a 26-week randomized treatment period and an extension period during which all patients received ravulizumab for up to 2 years.[8] Patients were stratified according to transfusion history.[8] Patients assigned to the ravulizumab treatment group received weight-based dosing: a loading dose on day 1 followed by maintenance doses of ravulizumab on day 15 and every 8 weeks thereafter.[8] Patients assigned to eculizumab received a maintenance dosage of 900 mg every 2 weeks.[8] At the end of the 26-week treatment period, ravulizumab-treated patients continued weight-based maintenance dosing of ravulizumab, whereas eculizumab-treated patients were switched to open-label ravulizumab for the extension period.[8]

The primary efficacy end point was hemolysis, as measured by percentage change in LDH from baseline to day 183.[8] Key secondary end points included proportion of patients with breakthrough hemolysis, change in FACIT–Fatigue score, transfusion avoidance, and stabilized hemoglobin.[8] In stable patients previously treated with eculizumab, the mean percentage change in LDH in ravulizumab and eculizumab treatment arms was − 0.82% versus + 8.39% [treatment difference of 9.21% (95% CI − 0.42 to 18.84); p<0.0006 for noninferiority].[8] The lower bound of the 95% CI for the difference was −0.42%, which did not exceed the protocol-specified noninferiority margin of −15%, indicating that ravulizumab is noninferior to eculizumab.[8] In 191 patients completing 183 days of treatment, ravulizumab was noninferior to eculizumab for outcomes of breakthrough hemolysis (difference, 5.1 [95% CI, −8.89 to 18.99]), change in FACIT-Fatigue score (difference, 1.47 [95% CI, −0.21 to 3.15]), transfusion avoidance (difference, 5.5% [95% CI, −4.27 to 15.68]), and stabilized hemoglobin (difference, 1.4% [95% CI, −10.41 to 13.31]; p<0.0006 for noninferiority for all end points).[8]

Transfusion avoidance in ravulizumab and eculizumab treatment arms in the trial in patients previously treated with eculizumab was achieved in 87.6% of patients receiving ravulizumab and 82.7% receiving eculizumab [treatment difference 5.5% (95% CI − 4.27 to 15.68)].[8] Results of this trial also demonstrated that patients with PNH can be effectively and safely switched from eculizumab every 2 weeks to ravulizumab every 8 weeks.[8] Compared to eculizumab, ravulizumab

was noninferior for achieving transfusion independence, LDH normalization, the proportion of patients with breakthrough hemolysis, change in serum free C5, and fatigue score.[7] Safety and tolerability of were similar, and no meningococcal infections occurred with either therapy.

Trial Limitations

Both of the phase 3 trials that evaluated the efficacy of ravulizumab were noninferiority trials, which are not designed to show superiority of one drug over another. In both trials ravulizumab provided similar efficacy as eculizumab in treating PNH in patients that were C5 naïve or who had previous exposure to C5 treatment. Both trials were relatively short-term considering PNH is a chronic condition. Finally, both trials were designed, conducted and funded by the manufacturer.

Atypical Hemolytic Uremic Syndrome

A prospective, open-label, phase 3 trial evaluated the efficacy and safety of ravulizumab in adults with aHUS.[9] In this global, multicenter, single arm study, patients received intravenous ravulizumab as a weight-based loading dose on day 1, followed by weight-based maintenance doses on day 15 and every 8 weeks thereafter.[9] After 26 weeks of treatment with ravulizumab, complete thrombotic microangiopathy response (TMA; primary efficacy endpoint) was seen in 53.6% of complement-inhibitor naïve adult patients with aHUS (n =56).[9] A complete TMA response encompasses hematological normalization [reduced thrombocytopenia (evidenced by normalization of platelet count) and hemolysis (normalization of LDH levels)] and improved renal function (≥ 25% improvement in serum creatinine level from baseline).[9] Thrombocytopenia was reduced in 83.9% (95% CI 73.4–94.4%) of patients, LDH levels were normalized in 76.8% (95% CI 64.8–88.7%) and improved renal function was seen in 58.9% (95% CI 45.2–72.7%).[9] Due to the high risk of bias (single-arm, open label, non-randomized, small sample size) in this trial, it is not presented in **Table 9** (Comparative Evidence Table).

Clinical Safety:

In the United States, ravulizumab is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.[10] Ravulizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections.[10] Common adverse effects associated with ravulizumab administration may include upper respiratory tract infection and headache.[10] Serious adverse reactions were reported in 15 (6.8%) patients with PNH receiving ravulizumab.[10] The serious adverse reactions in patients treated with ravulizumab included hyperthermia and pyrexia.[10] No serious adverse reaction was reported in more than 1 patient treated with ravulizumab.[10] Adverse reactions reported in clinical trials in patients with PNH and aHUS are presented in **Tables 6 and 7.**

Table 6. Adverse Reactions Reported in 5% or More of Ravulizumab-Treated Patients with PNH Compared with Eculizumab[10]

Adverse Reaction	Ravulizumab (n=222)	Eculizumab (n=219)
Upper Respiratory Tract Infection	86 (39%)	86 (39%)
Headache	71 (32%)	57 (26%)
Diarrhea	19 (9%)	12 (5%)
Nausea	19 (9%)	19 (9%)
Pyrexia	15 (7%)	18 (8%)
Abdominal Pain	13(6%)	16 (7%)

Table 7. Adverse Reactions Reported in 10% or More of Ravulizumab-Treated Patients with aHUS[10]

Adverse Reaction	Ravulizumab (n=16)
Pyrexia	8 (50%)
Upper Respiratory Tract Infection	7 (44%)
Diarrhea	6 (38%)
Headache	5 (31%)
Abdominal Pain	3(19%)
Nausea	2 (13%)

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

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Hemolysis
2) Percentage of patients with breakthrough hemolysis
3) Anemia
4) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Proportion of patients that were transfusion free (PNH)
2) Percentage change in LDH levels from baseline (PNH)
3) Complete thrombotic microangiopathy response (aHUS)

Table 8. Pharmacology and Pharmacokinetic Properties[10]

Parameter	
Mechanism of Action	Complement C5 Inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution = 5.34 L (PNH) and 5.22 L (aHUS)
Elimination	29.5 L/day (PNH) and 53.3 L/day (aHUS)
Half-Life	49.7 days (PNH) and 51.8 days (aHUS)
Metabolism	N/R

Abbreviations: aHUS = atypical Hemolytic Uremic Syndrome; L=Liters; N/A = Not Applicable; N/R = Not Reported; PNH=Paroxysmal Nocturnal Hemoglobinuria

Table 9. 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. Lee JW, et al.[7] OL, MC, phase 3 NI study over 183 days	1. Weight based ravulizumab induction followed by maintenance dose administered IV every 8 weeks 2. Eculizumab 900 mg IV administered every 2 weeks	Demographics: 1.Male: 55% 2.Age: 46 yo 3. Race: White: 38% Asian: 52% Japanese: 14% Black: 2% 4. Percent of patients with transfusions received 1 year prior to first study dose: 13% Key Inclusion Criteria: 1. Adults ≥ 18 yo with PNH, naive to C5 treatment 2.LDH ≥ 1.5 ULN Key Exclusion Criteria: 1.Previous C5 exposure 2.Weight < 40 kg 3. History bone marrow transplantation 4.Platelet count < 30,000/μL	ITT: 1. 125 2. 121 PP: 1.125 2.119 Attrition: 1. 0 (0%) 2. 3 (2%)	Co-Primary Endpoint: a. Proportion of patients that were transfusion-free at 26 weeks 1. 92 (73.6%) 2. 80 (66.1%) Difference: 6.8% (95% CI, -4.66 to +18.14) P<0.0001 for NI b. LDH normalization from days 29 through 183 1. 67 (53.6%) 2. 60 (49.4%) OR: 1.19 95% CI 0.80 to 1.77 P<0.0001 for NI Secondary Endpoints: a. LSM change in LDH 1.-76.84 2.-76.02 Mean Difference: -0.83% 95% CI -5.21 to 3.56 P<0.0001 for NI b. LSM change in FACIT-Fatigue score from baseline 1. 7.70 2. 6.40 Difference: 0.67 95% CI -1.21 to 2.55 P<0.0001 for NI	N/A for all due to NI study design	Serious Adverse Effects 1. 4 (3%) 2. 8(7%) Adverse Effects: 1. 110 (88%) 2. 105 (87%) Headache: 1. 45 (36%) 2. 40 (33%) Nasopharyngitis 1. 11 (8.8%) 2. 18 (14.9%) Upper Respiratory Infection 1. 13 (10%) 2. 7 (6%) 95% CI and p-value NR for all	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 to receive ravulizumab or eculizumab. Method of randomization not described. Baseline characteristics balanced between groups. Performance Bias: High. Study was not blinded. Detection Bias: High. Open label study design Attrition Bias: Low. Attrition rates were low in both arms. Reporting Bias: Low. Protocol available online at clinicaltrials.gov. Outcomes reported as prespecified. Other Bias: Unclear. Funded by Alexion Pharmaceuticals, Inc. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol **Applicability**: Patient: Patients naïve to C5 therapy Intervention: Dosing evaluated in phase 2 trial Comparator: Noninferiority comparison with eculizumab. Outcomes: Transfusion requirements and elevated hemolysis (LDH≥1.5 x ULN) are significant measures of PNH disease severity. Setting: 123 centers in 25 countries

2. Kulaesekaraj AG, et al.[8] OL, MC, phase 3 NI study over 183 days	1. Weight based ravulizumab induction followed by maintenance dose administered IV every 8 weeks 2. Eculizumab 900 mg IV administered every 2 weeks	Demographics: 1.Male: 50% 2.Age: 48 yo 3. Race: White: 57% Asian: 22% Japanese: 6% Black: 4% Key Inclusion Criteria: 1. Adults ≥ 18 yo with PNH, previously treated with eculizumab 2. LDH level ≤1.5 x the ULN (ULN: 246 U/L Key Exclusion Criteria: 1. LDH >2 x ULN 2. Platelet count < 30,000/µL 3. Weight < 40 kg 4. History bone marrow transplantation	ITT: 1. 97 2. 98 PP: 1. 96 2. 95 Attrition: 1. 1 (1%) 2. 3 (3%)	Primary Endpoint: LSM percentage change in LDH from baseline through day 183 1. -0.82% 2. +8.4% Difference: 9.2% 95% CI: -0.42% to +18.8% p<0.0006 for NI Secondary Endpoints: a. Proportion of patients that were transfusion-free 1. 85 (87.6%) 2. 74 (75.2%) Difference: 5.5% (95% CI, -4.3 to +15.7) P<0.0006 for NI b. LSM change in FACIT-Fatigue score from baseline 1. 2.0 2. 0.54 Difference: 1.5 95% CI -0.2 to 3.2 P<0.0006 for NI	N/A for all due to NI study design	Adverse Effects: 1. 85 (87.6%) 2. 86 (87.8%) Headache: 1. 26 (26.8%) 2. 17 (17.3%) Nasopharyngitis 1. 21 (21.6%) 2. 20 (20.4%) Upper Respiratory Infection 1. 18 (18.6%) 2. 10 (10.2%) 95% CI and p-value for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Assigned 1:1 to ravulizumab or eculizumab. Method of randomization not described. Baseline demographics balanced between groups Performance Bias: High. Study was not blinded. Detection Bias: High. Open label study design. Attrition Bias: Low. Attrition rates were low in both arms. Reporting Bias: Low. Protocol available online at clinicaltrials.gov. Outcomes reported as prespecified. Other Bias: Unclear. Funded by Alexion Pharmaceuticals, Inc. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol. **Applicability**: Patient: Patients previously exposed to C5 therapy Intervention: Dosing evaluated in phase 2 trial Comparator: Noninferiority comparison with eculizumab. Outcomes: Hemolysis (as assessed by LDH levels) is a significant measure of PNH disease severity Setting: 49 centers in 11 countries

Abbreviations: ARR = absolute risk reduction; C5 = complement 5; CI = confidence interval; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; ITT = intention to treat; IV = intravenous; LDH = lactate dehydrogenase; LSM = least squares mean; MC = multi-center; N = number of subjects; NA = not applicable; NI = Non-Inferiority; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PP = per protocol; ULN = upper limit of normal

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
eculizumab	SOLIRIS	INTRAVEN	VIAL	
ravulizumab-cwvz	ULTOMIRIS	INTRAVEN	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 15, 2021.

1. *exp Hemoglobinuria, Paroxysmal/ 1691*
2. *exp Atypical Hemolytic Uremic Syndrome/ 687*
3. *exp Myasthenia Gravis/ 7030*
4. *eculizumab.mp. 1792*
5. *ravulizumab.mp. 39*
6. *1 or 2 or 3 9374*
7. *4 or 5 1799*
8. *6 and 7 713*
9. *limit 8 to (english language and humans) 632*
10. *limit 9 to (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 controlled clinical trial or guideline or meta-analysis or randomized controlled trial or "systematic review") 38*

Appendix 3: Prescribing Information Highlights

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

SOLIRIS® (eculizumab) injection, for intravenous use
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection.)**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

  Limitation of Use
  Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive (1.3).
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG and NMOSD Dosage Regimen: (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.1).
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain (6.1).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ULTOMIRIS® (ravulizumab-cwvz) injection, for intravenous use
Initial U.S. Approval: 2018

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risks of developing a meningococcal infection. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infection. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program (5.1).

RECENT MAJOR CHANGES

Dosing and Administration (2.5) 10/2020

INDICATIONS AND USAGE

ULTOMIRIS is a complement inhibitor indicated for:

- the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) (1).
- the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) (1).

Limitations of Use:
ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

DOSAGE AND ADMINISTRATION

See Full Prescribing Information for instructions on dosage, preparation, and administration (2.1,2.2, 2.3, 2.4, 2.5).

DOSAGE FORMS AND STRENGTHS

Injection:

- 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).
- 300 mg/3 mL (100 mg/mL) in a single-dose vial (3).
- 1,100 mg/11 mL (100 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

ULTOMIRIS is contraindicated in:

- Patients with unresolved *Neisseria Meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection (4, 5.1).

WARNINGS AND PRECAUTIONS

- Other Infections: Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).
- Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures (5.5).

ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence ≥10%) were upper respiratory tract infection and headache (6.1).

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2020

Eculizumab (Soliris®)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is FDA-approved for:
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
  - Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AchR) antibody positive

Length of Authorization:

Up to 12 months

Requires PA:

- Soliris® (eculizumab) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Has the patient been vaccinated against *Neisseria meningitides?*	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis one of the following: • Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), OR • atypical Hemolytic Uremic Syndrome (aHUS)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the requested dosing align with the FDA- approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for a diagnosis of myasthenia gravis ACh Receptor (AChR) antibody-positive?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient tried: • at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR • at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab[1]

	Eculizumab (Soliris®)
FDA-approved Indications	• Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody • Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) • Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive
Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter
Recommended aHUS dose in patients less than 18 yo	Weight based: refer to prescribing information for dosing in pediatric patients
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter
Recommended generalized MG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter

Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)

1. Soliris (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 4/21 (DM)
Implementation: TBD

Ravulizumab (Ultomiris®)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Ravulizumab is FDA-approved for:
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)

Length of Authorization:

Up to 12 months

Requires PA:

- Ultomiris® (Ravulizumab) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 4
4. Has the patient been vaccinated against *Neisseria meningitides?*	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis for a patient with Paroxysmal Nocturnal Hemoglobinuria (PNH) or atypical Hemolytic Uremic Syndrome (aHUS)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Does the requested dosing align with the FDA-approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Ravulizumab[1]

	Ravulizumab		
FDA-approved Indications	• Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)		
Recommended aHUS dose in patients less than 18 yo	Weight based: refer to prescribing information for dosing in pediatric patients		
Recommended aHUS dose in patients 18 yo and older	**Body Weight** 40-59 kg 60-99 kg ≥ 100 kg	**Loading Dose** 2,400 mg 2,700 mg 3,000 mg	**Maintenance Dose** 3,000 mg every 8 weeks 3,300 mg every 8 weeks 3,600 mg every 8 weeks
Recommended PNH dose in patients 18 yo and older	**Body Weight** 40-59 kg 60-99 kg ≥ 100 kg	**Loading Dose** 2,400 mg 2,700 mg 3,000 mg	**Maintenance Dose** 3,000 mg every 8 weeks 3,300 mg every 8 weeks 3,600 mg every 8 weeks

1. Ultomiris™ (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 10/2020.

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 Update: Statins & Combos (High Potency & Low-Medium Potency)

Date of Review: April 2021

Date of Last Review: January 2015
Dates of Literature Search: 07/25/2014 – 12/31/2020

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

Purpose for Class Update:
To search for and evaluate new comparative evidence for the efficacy and safety of statin therapy in reducing cardiovascular (CV) outcomes or mortality in adults with CV disease or at high risk for CV disease.

Research Questions:
- Is there any new comparative evidence for statin lipid-lowering agents in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of CV disease?
- Is there any new comparative evidence for the harms of statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
- Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one statin agent is more effective or associated with more harm than other statin agents?

Conclusions:
- There is high quality evidence that statins reduce all-cause mortality and CV events (i.e. non-fatal myocardial infarction [MI], coronary death, non-fatal stroke) compared to placebo in patients with clinical atherosclerotic cardiovascular disease (ASCVD) (i.e. acute coronary syndrome [ACS], history of MI, unstable angina, stroke, and symptomatic peripheral artery disease [PAD]).
- There is low quality evidence that high intensity statin dosing reduces non-fatal CV events compared to moderate intensity statins in patients with ASCVD, but no benefit in overall mortality or CV mortality.
- There is high quality evidence that moderate-dose statins lower CV mortality, CV events and all-cause mortality in the primary prevention of ASCVD, with greater absolute benefits in patients at higher baseline CV risk. There is insufficient evidence demonstrating a larger benefit with high-dose statins in the primary prevention population.
- There is moderate quality evidence of no difference in proportional effects of statins between men and women and low-quality evidence no differences in efficacy or safety based on other subgroups, including age, race, baseline lipid levels, presence of diabetes or hypertension.

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- There is insufficient evidence of a significant difference in effectiveness on clinical outcomes between statin drugs. Instead, benefit depends on LDL-c lowering ability and baseline risk.
- There is moderate quality evidence of a higher risk of discontinuations due to adverse events, new onset diabetes mellitus and elevations in aminotransferases without reports of liver failure with high dose statins compared to control or lower dose statins.

Recommendations:
- Continue to maintain preferred statins that offer low-, moderate- and high-intensity statins for both the primary and secondary prevention of ASDVD as well as for individuals at a higher risk of statin associated adverse events.
- Combine high potency and low-medium potency PDL classes into one PDL statin class
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy:
- Evidence supports the use of statins for the primary prevention of cardiovascular disease (CVD) with a demonstrated reduction in all-cause mortality (RR 0.86, 95% CI 0.79-0.94, NNT 96), fatal CVD events (RR 0.83, 95% CI 0.72-0.96), and fatal coronary heart disease (RR 0.82, 95% CI 0.70-0.96).
- There is moderate quality evidence of an increased risk of developing diabetes mellitus (RR 1.18, 95% CI 1.01-1.39) with statin therapy compared to placebo.
- There is evidence that statin therapy is not associated with an increased risk of cancer (RR 1.16, 95% CI 0.87-1.54).
- There is insufficient comparative evidence on long term clinical outcomes or evidence that one statin agent is safer than another.

Background:
The association between hypercholesteremia, and particularly elevated low-density lipoprotein (LDL) cholesterol, and cardiovascular disease (CVD) is well established.[1] In addition to optimizing a healthy lifestyle, prevention of CV events involves optimization of treatments that have proven benefits on reduction in CV events and/or cardiovascular (CV) mortality. Statins have strong and consistent evidence demonstrating CV risk reduction. For every reduction of 39 mg/dl in low density lipoprotein cholesterol (LDL-C), statins can provide relative reductions in CV events by 22% and all-cause mortality of 10%.[1] Statin therapy remains the pharmacologic cornerstone to lower LDL-C levels and is therefore used in the treatment of both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). However, dose escalation and/or combination with non-statin therapy to reduce ASCVD risk may be necessary for high-risk populations.[2]

Statins are competitive inhibitors of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibits the rate controlling step in cholesterol synthesis.[1] Absolute benefit of therapy with statins depends more on an individual's baseline CV risk, rather than cholesterol levels. Guidelines recommend statin therapy based on the LDL lowering ability (**Table 1**).[2,3] Moderate intensity statins are recommended in most patients and can lower the LDL-C by 30-49%. For high-risk individuals who may benefit from further LDL-lowering, high intensity dosing is recommended, which can lower the LDL-C by more than 50%. There does not seem to be significant differences in efficacy between different statins. The most common side effect reported with statin therapy is myalgia. However, the risk of rhabdomyolysis and serious liver injury is low and there remains debate on how much of the reported myalgia side effects are due to a nocebo effect.[4] For statin intolerant patients, lower doses or alternative dosing strategies of statins are recommended.

Current guidelines recommend at least moderate intensity statins as first line therapy for those with clinical ASCVD, severe hypercholesterolemia (LDL-C > 190), and in those with diabetes.[2] For the primary prevention of CVD in those without diabetes, there is some debate on when to initiate therapy based on the

American College of Cardiology / American Heart Association (ACC/AHA) pooled cohort equation. A shared decision-making strategy and consideration of additional risk factors is recommended prior to initiating treatment for primary prevention. Guideline recommendations vary between statin consideration with a 10-year ASCVD of at least 7.5%, 10% or 12% depending on the guideline.[2,5,6] However, they are all consistent with recommendations to use a shared-decision making strategy, consideration of additional risk factors and harms, and that the benefit risk profile is unclear in people 75 years and older and younger than 40 years without clinical ASCVD.

Table 1: Statin Intensity[2]

	LDL-C reduction	Drug and Dose
High-intensity	≥ 50%	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg
Moderate-intensity	30 to 49%	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40mg-80mg Fluvastatin 40 mg BID Pitavastatin 1-4mg
Low-intensity	<30%	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

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:
After review, 11 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria)[7-9],[10], wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[11-13] or outcome studied (e.g., non-clinical). Systematic reviews evaluating the effect on LDL-C but not cardiovascular events were not included.[14-18]

Secondary Prevention
A meta-analysis included RCTs comparing either statin to placebo or standard to intensive statin treatment for the secondary prevention of CV and cerebrovascular events in patient with diabetes.[19] Only high quality, double-blind studies were included, and studies were assessed for quality using the Jadad score. Nine RCTs were included; five comparing standard dose statin with placebo and four comparing intensive-dose to standard dose statin. For the comparison of standard-dose statin versus placebo, the authors found a NNT of 27 over 5 years to prevent one major CV or cerebrovascular event (RR 0.85; 95% CI 0.79 to 0.91). [19] There was no significant difference in all-cause mortality (RR 0.78; 95% CI 0.53-1.14). Compared to standard dose-statin, there was a significant reduction in major CV events with intensive dose statin over 5 years (34.9% vs. 31.7%, respectively; RR 0.91; 95% CI 0.84 to 0.98). [19] Standard dose statins included pravastatin 40 mg, atorvastatin 10 mg and simvastatin 20 mg daily. The intensive-dose statin groups were treated with simvastatin 80 mg or atorvastatin 80 mg. The data were insufficient to compare standard dose to intensive dose treatment for secondary endpoints in meta-analysis, including all-cause and CV mortality. [19]

A systematic review attempted to evaluate the impact of more-intensive vs. less-intensive LDL-C lowering with pharmacologic treatment, including statins, in patients with established ASCVD.[20] A literature search was done to identify trials with > 500 patients evaluating CV outcomes during at least 1-year follow up. The Cochrane risk of bias assessment tool was used to evaluate the risk of bias among included trials. A total of 19 trials met inclusion criteria, including 15 trials of statins. Risk of bias was rated as low in all studies. Overall, there was a significant reduction in major vascular events with more-intensive treatment compared to less-intensive treatment (RR 0.81; 95% CI 0.77-0.86). [20] More intensive vs. less-intensive included statin vs. no statin, more-statin vs. less-statin and non-statin in combination with statin compared to statin plus placebo. The benefit was greater in trials comparing statin vs. no statin (RR 0.77; 95% CI 0.71-0.83) than in trials of more-statin vs. less-statin (RR 0.88; 95% CI 0.82-0.93) or in trials of non-statin vs. placebo (RR 0.85; 95% CI 0.77-0.95). [20] There was a significant reduction in all-cause (RR 0.85; 95% CI 0.78 to 0.92) and CV mortality (RR 0.78; 95% CI 0.73 to 0.84; I^2 3%) with statin compared to no statin. However, there was no survival benefit with more intensive statin compared to less intensive statin treatment.

Authors of a recent meta-analysis searched all RCTs comparing more- (intensive statin therapy or combination therapy with ezetimibe or PCSK9 inhibitor on top of statin) and less-intensive therapy on CV outcomes.[21] The Cochrane risk of bias tool was used to assess quality of each trial. The primary outcome was major adverse cardiovascular events (MACEs) or equivalent. Twenty-three studies (n=133,037) studies were included. Twelve evaluated more intensive versus less intensive statins and will be the focus of this review. The majority of included patients had coronary artery disease (CAD) and follow up duration ranged from 0.8 to 6.7 years. Overall, more intensive therapy (intensive statin, ezetimibe, or PCSK9 inhibitor) reduced the odds of MACE compared to less intensive therapy (odds ratio [OR] 0.84; 95% CI 0.79 to 0.88). [21] Additionally, more intensive statin therapy reduced the odds of MACE compared to less intensive statin therapy (OR 0.83; 95% CI 0.76 to 0.90). [21] For safety outcomes, there was no significant difference in rhabdomyolysis (RR 1.72; 95% CI 0.52 to 5.68) between higher-dose statin and lower dose, with a wide confidence interval. There was an increase in elevation of aminotransferases (RR 2.89; 95% CI 1.51 to 5.53). [21] There was moderate heterogeneity among the trials for MACE.

Primary Prevention

A systematic review and evidence report to inform the US Preventive Services Task Force (USPSTF) guidelines reviewed the benefits and harms of statins for prevention of CVD in adults without prior CV events (primary prevention).[22] Studies were limited to those in which fewer than 10% of the participants had a history of CV events. Studies comparing statin to placebo or no statin, and studies evaluating the effects of statin therapy intensity were included. Nineteen RCTs were identified comparing statins on clinical outcomes in adults without a history of CV events (n=71,344). [22] Mean ages ranged from 51 to 66 years and duration of follow-up ranged from 6 months to 6 years. All trials enrolled patients at increased CV risk (i.e. presence of dyslipidemia, early cerebrovascular disease, diabetes, or hypertension). Six trials were rated as good quality, 12 of fair quality and one trial was poor quality because it did not report attrition. Statins were associated with reduced risk in all-cause mortality compared to placebo (RR 0.86; 95% CI 0.80 to 0.93; absolute risk difference [ARD] -.4%; 95% CI -0.64%--0.17%; I^2=0%) and CV mortality (RR 0.82; 95% CI 0.71 to 0.94; ARD -.2%; 95% CI -0.35%--0.05%; I^2=0%). [22] There were no differences in relative risk estimates based on sex, age, race/ethnicity, or baseline lipid levels, but absolute benefits were greater in subgroups at higher risk for events. There was no significant difference in withdrawals due to adverse events with statins compared to placebo (RR 0.95; 95% CI 0.75 to 1.21; I^2=86%). [22] There was also no significant difference in serious adverse events, any cancer, fatal cancer, myalgias, rhabdomyolysis or elevated aminotransferase levels. Statins were not associated with increased risk of diabetes compared to placebo (RR 1.05; 95% CI 0.91 to 1.20). However, most studies did not include high intensity dosing because of the low baseline risk of the population. The studies comparing different intensities were underpowered to evaluate clinical outcomes.

Primary and Secondary Prevention

A meta-analysis of studies included in the Cholesterol Treatment Trialists' (CTT) Collaboration aimed to evaluate the effects of statin therapy on CV outcomes in men and women in both primary and secondary prevention.[23] Estimates of the mean effect on lipid concentration between women and men were compared using a t-test. Individual participant data were available from 27 trials of statin therapy. Twenty-two trials compared statin therapy to control and 5 trials compared more-intensive statin therapy to less-intensive. Overall, 26.8% (n=46,675) of all participants were women. The mean duration of follow up was 4.9 years (ranging from 2 to 7 years). Mean concentrations of total and LCL-C at baseline were similar in men and women but all baseline characteristics differed significantly. Women were older and had a higher prevalence of hypertension and diabetes and were less likely to smoke. Statins reduced the risk of major CV events by 21% for each 1 mmol/L (38.8 mg/dl) reduction in LDL-C with significant reductions in both women and men (rate ratio 0.79; 95% CI 0.77-0.81). [23] After adjusting for other differences in baseline characteristics, there was no heterogeneity (p=0.331) between proportional effects of statins in women (RR 0.84; 99% CI 0.78 to 0.91) and men (RR 0.78; 99% CI 0.75 to 0.81). [23] Effects in participants without a history of vascular disease were slightly greater in men (RR 0.72; 99% CI 0.66 to 0.80) than women (RR 0.85; 99% 0.72 to 1.00) but were similar in those treated for secondary prevention.

A systematic review was done to compare standard-dose statin and high-dose statin treatment for stroke prevention in adults with and without ASCVD (primary and secondary prevention).[24] Only RCTs with masked assessment of outcomes were included. Standard treatment was defined as doses less than or equal to atorvastatin 20mg, simvastatin 60 mg, rosuvastatin 10 mg or any dose of pravastatin, lovastatin or fluvastatin. Seventeen RCTs (n=120,970) were included in the analysis. Seven trials compared placebo or standard-dose statin with intensive-dose statin treatment and 10 studies compared standard-dose treatment with placebo. No studies included lovastatin as a treatment arm and the majority included atorvastatin (n=9). Intensive-dose statin treatment resulted in a significant reduction in all-stroke incidence (RR 0.79; 95% CI 0.71 to 0.87) compared to placebo or standard dose (2.4% vs. 3.1%, respectively) with nonsignificant heterogeneity and no significant reporting bias. There was also a significant reduction in fatal stroke with intensive-dose statin (RR 0.61; 95% CI 0.39 to 0.96). [24] There was an increase in the risk of elevated aminotransferases with intensive-dose statin treatment compared to standard dose or placebo (RR 5.45; 95% CI 3.81 to 7.81). [24]

Familial Hypercholesterolemia

A Cochrane Collaboration systematic review assessed the effectiveness and safety of statins in children with heterozygous familial hypercholesterolemia (HeFH).[25] Since mortality and non-fatal CV events are rare in children, the primary outcomes were surrogate outcomes, including change in serum LDL-C, change in carotid intima-media thickness and change in measures of growth maturation. Secondary outcomes included liver dysfunction, myopathy and rhabdomyolysis. Nine RCTs met inclusion criteria (n=1177). Median follow up time was only 24 weeks (range from 6 weeks to 2 years). Age of study participants ranged from 6 to 18 years. Five studies reported change in serum LDL-C (high quality evidence) and demonstrated a 32.15% (95% CI 34.9%-29.4%) mean reduction with statins compared to placebo. [25] Despite some risk of bias concerns, evidence was rated high quality due to the large effect size. There was low quality evidence in no difference in the number of cases of either liver dysfunction (increase in aminotransferase levels greater than 3 times the upper limit of normal) or myopathy between statins and placebo. However, the confidence intervals of pooled results were wide due to very low number of events. There were no reported cases of rhabdomyolysis. There was moderate quality evidence of no difference in adverse events at 1 year between statins and placebo (RR 1.01; 95% CI 0.81 to 1.26). [25]

Harms

A systematic review evaluated evidence for an association between statin therapy and impaired cognition from RCTs.[26] RCTs comparing statin therapy to placebo or standard therapy and reported cognitive outcomes were included. Cochrane risk of bias tool was used to determine study quality. Twenty-five RCTs were included and all were placebo-controlled. Duration varied between 2 weeks and 260 weeks. The majority of studies included participants with normal cognition at baseline and risk of bias ranged from low to moderate for most studies. Sixteen studies reported cognitive test outcomes using various tests and data from 14 of the studies was able to be combined in meta-analysis. There was no statistically significant difference between statin and no statin groups on cognitive outcomes (standard mean difference [SMD] 0.01; 95% CI 0.01 to 0.03). [26] However, effect sizes were combined across various cognition domains, which is difficult to interpret.

A systematic review and meta-analysis was done to compare the tolerability and safety of long-term (>6 weeks) treatment with high-intensity atorvastatin 80 mg daily.[27] RCTs published through 2015 reporting safety outcomes with atorvastatin 80 mg were identified and the Cochrane risk of bias tool was used to assess quality. Seventeen studies met selection criteria and were included in the meta-analysis. Mean age in the trials ranged from 43 to 75. Thirteen studies provided moderate evidence that atorvastatin 80 mg/day was significantly less well-tolerated leading to discontinuations due to adverse events compared with the control (placebo or lower dose atorvastatin) (8.8% vs. 6.8% RR 1.29; 95% CI 1.17-1.42) with no significant heterogeneity. [27] There was high quality evidence of a higher risk of elevations in liver transaminases (1.6% vs. 0.3%; RR 4.59; 95% CI 3.26-6.48) and low quality evidence of no difference in myalgia (RR 1.06; 95% CI 0.93-1.20). [27] There were few older participants > 75 years of age, limiting the generalizability to this population at higher risk of adverse events.

New Guidelines:

Department of Veterans Affairs

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work group updated the guidelines for the management of dyslipidemia for cardiovascular risk reduction in 2020.[3,6] This is a high-quality guideline designed to assist primary care providers in managing dyslipidemia for the purpose of CVD risk reduction. Similar to ACC/AHA guidelines for the management of cholesterol, statins are the recommended first-line therapy for patients with CVD and for those at high risk of CVD. They also recommend treating based on target medication doses used in clinical trials rather than treating toward target LDL-C levels. The following recommendations regarding statin therapy are included in the update:

- For secondary prevention, at least a moderate-dose statin is recommended (Strong Recommendation)
    - This recommendation came from three meta-analyses from the CTT Collaborators showing fixed-dose moderate intensity statins (simvastatin 20-40 mg, pravastatin 40 mg, lovastatin 20-80, and atorvastatin 10 mg) led to a reduction in all-cause mortality, non-fatal MI, coronary death and non-fatal stroke when compared to placebo.
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest offering high-dose statins for reducing non-fatal CV events after discussion of the risk of high dose statins and an exploration of the patient's values and preferences (Weak recommendation)
    - This recommendation differs from the ACC/AHA guidelines and is supported by meta-analyses that only demonstrated an incremental benefit for a reduction in non-fatal events (e.g., MI, stroke), but no significant reduction in CV or all-cause mortality when comparing high-dose statins to lower doses statins.
    - There is a high risk of statin-related adverse events and more discontinuations due to adverse events with high dose statins compared to lower dose statins.
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest adding ezetimibe to either moderate- or high-dose statins for reducing non-fatal cardiovascular events following a discussion of the risks, additional benefits, and an exploration of the patient's values and preferences (Weak recommendation)
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest offering a PCSK9 inhibitor in addition to a maximally tolerated statin dose with ezetimibe for reducing non-fatal cardiovascular events following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient's values and preferences (Weak recommendation)
- For primary prevention, a moderate-dose statin is recommended for those with a 10-year CV risk greater than 12% or LDL-C $\geq$ 190 mg/dl or diabetes (Strong recommendation)
- For primary prevention, they suggest offering a moderate-dose statin for patients with a 10-year cardiovascular risk between 6% and 12% following a discussion of risks, limited benefit, and an exploration of the patient's values and preferences (Weak recommendation)

Guidelines included for clinical context only:

American College of Cardiology / American Heart Association

Updated recommendations for reducing ASCVD risk were released following from the American College of Cardiology (ACC) / American Heart Association (AHA) in 2018.[2] Guidelines were updated based on a systematic review that identified 10 new RCTs in patients with clinical ASCVD or at high risk of ASCVD. The prespecified primary outcome was a composite of fatal CV events, nonfatal MI, or nonfatal stroke. RCTs were assessed for bias using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis was not done, and direct comparisons of the included RCTs could not be performed. This guideline was evaluated and reviewed in previous reviews for the non-statin dyslipidemia PDL class in in May 2019.

Overall, statins are recommended in all patients with ASCVD and at high risk for ASCVD. Statins are recommended in the four patient management groups, which were modified from previous guidelines to allow for more personalized care and more detailed risk assessments (**Table 2).**

Table 2: Patient Management Groups

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin (≤ 75 y/o); moderate- to high-intensity statin if > 75 y/o
Severe Hypercholesterolemia (LDL-C ≥ 190 mg/dl)	Maximally tolerated statin
Diabetes age 40-75 and LDL-C ≥ 70 mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
Primary Prevention (Adults 40-75 years with LDL-C ≥70)	Moderate- intensity statin based on risk discussion, 10-year ASCVD risk, and ASCVD risk enhancers
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; y/o: years old	

A significant change in the guidelines is the addition of an LDL-C threshold of 70 mg/dl to consider adding a non-statin in clinical ASCVD. This recommendation comes from the general idea that "lower is better" for LDL-C, particularly in high-risk patients. Very high-risk ASCVD is a new category and includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a PCSK9 inhibitor if LDL-C remains ≥ 70 mg/dl on both statin and ezetimibe therapy for very high-risk patients only.

New Formulations or Indications:

In 2017, the FDA approved pitavastatin magnesium (Zypitamag®) for use in adults with primary hyperlipidemia or mixed dyslipidemia. The magnesium salt formulation was considered bioequivalent to pitavastatin calcium (Livalo®).[28]

In November 2015, rosuvastatin was FDA approved for pediatric patients age 8 to 17 years with heterozygous familial hypercholesterolemia.[29] Previously it was only approved for age 10 years and up. In 2016, the label was further expanded to include pediatric patients aged 7 to 17 years with homozygous familial hypercholesterolemia.[29] These approvals were based on studies demonstrating safety and LDL-C lowering ability in this pediatric populations.[30,31]

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)
Simvastatin[32]	Zocor	3/2019	Warnings	Chinese patients may be at a higher risk of myopathy
Rosuvastatin Fluvastatin Simvastatin	Crestor Lescol Zocor	9/2020	Warnings and Precautions	Immune-mediated necrotizing myopathy

Randomized Controlled Trials:

A total of 266 citations were manually reviewed from the initial literature search and 11 were evaluated more carefully for inclusion. After further review, 10 citations were excluded because of wrong study design (eg, observational)[33-35], comparator (eg, no control or placebo-controlled)[36-39], or outcome studied (eg, non-clinical)[40-42]. The remaining 2 trials are summarized in the table below and systematic reviews were summarized above. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Stoekenbroek et al.[43]	Atorvastatin 80 mg/day (high dose) vs. simvastatin 20-40 mg/day (usual dose)	Post – MI patients	Incident PAD or recurrent PAD requiring hospitalization	<u>Incident PAD</u> Atorvastatin: 94 (2.2%) Simvastatin 135 (3.2%) HR 0.70; 95% CI 0.53 to 0.91
Berwanger, et al.[44] RCT, MC, PC	Atorvastatin 80 mg x 1, 40 mg daily x 7 days vs. placebo	Statin-naïve patients scheduled for a noncardiac surgery	Composite of all-cause mortality, nonfatal MI, and stroke at 30 days	<u>Composite CV outcome:</u> Atorvastatin: 54 (16.6%) Placebo: 59 (18.7%) HR 0.87; 95% CI 0.60-1.26 P=0.46

Abbreviations: CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; MC = multicenter; PAD = peripheral artery disease; PC = placebo-controlled; RCT = randomized clinical trial.

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Appendix 1: Current Preferred Drug List

High-Potency

Generic	Brand	Route	Form	PDL
atorvastatin calcium	ATORVASTATIN CALCIUM	ORAL	TABLET	Y
atorvastatin calcium	LIPITOR	ORAL	TABLET	Y
simvastatin	SIMVASTATIN	ORAL	TABLET	Y
simvastatin	ZOCOR	ORAL	TABLET	Y
ezetimibe/simvastatin	EZETIMIBE-SIMVASTATIN	ORAL	TABLET	N
ezetimibe/simvastatin	VYTORIN	ORAL	TABLET	N
pitavastatin calcium	LIVALO	ORAL	TABLET	N
pitavastatin magnesium	ZYPITAMAG	ORAL	TABLET	N
rosuvastatin calcium	EZALLOR SPRINKLE	ORAL	CAP SPRINK	N
rosuvastatin calcium	CRESTOR	ORAL	TABLET	N
rosuvastatin calcium	ROSUVASTATIN CALCIUM	ORAL	TABLET	N

Low-Medium Potency

Generic	Brand	Route	Form	PDL
lovastatin	LOVASTATIN	ORAL	TABLET	Y
pravastatin sodium	PRAVACHOL	ORAL	TABLET	Y
pravastatin sodium	PRAVASTATIN SODIUM	ORAL	TABLET	Y
fluvastatin sodium	FLUVASTATIN SODIUM	ORAL	CAPSULE	N
fluvastatin sodium	FLUVASTATIN ER	ORAL	TAB ER 24H	N
fluvastatin sodium	LESCOL XL	ORAL	TAB ER 24H	N
lovastatin	ALTOPREV	ORAL	TAB ER 24H	N

Appendix 2: Abstracts of Comparative Clinical Trials

- Stoekenbroek, et al. High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease. *Heart.* 2015 Mar;101(5):356-62

  Objectives: To study whether high-dose versus usual-dose statin treatment reduces the incidence of peripheral artery disease (PAD) and what is the effect of high-dose statin treatment on cardiovascular disease (CVD) outcome in patients with PAD.

  Methods and results: In the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial, 8888 post-myocardial infarction patients were randomised to high-dose or usual-dose statin therapy (atorvastatin 80 mg/day vs simvastatin 20-40 mg/day). We investigated the effect of high-dose versus usual-dose statins on the pre-specified outcome PAD incidence, and additionally performed a posthoc analysis of the efficacy of high-dose statins in reducing CVD risk among patients with PAD. During a median follow-up of 4.8 years, 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed PAD (HR=0.70, 95% CI 0.53 to 0.91; p=0.007). The risk of major coronary events was almost twofold higher in patients with PAD at baseline, but was no longer significant after adjusting for the adverse cardiovascular risk profile. In PAD patients, major coronary events occurred in fewer patients in the atorvastatin group (14.4%) than in the simvastatin group (20.1%), but the difference did not reach statistical significance. (HR=0.68, 95% CI 0.41 to 1.11; p=0.13). Atorvastatin treatment significantly reduced overall cardiovascular (p=0.046) and coronary events (p=0.004), and coronary revascularisation (p=0.007) in these patients.

  Conclusions: High-dose statin therapy with atorvastatin significantly reduced the incidence of PAD compared with usual-dose statin therapy with simvastatin. Patients with a history of PAD at baseline were at higher risk of future coronary events and this risk was reduced by high-dose atorvastatin treatment.

- Berwanger O, de Barros ESPG, Barbosa RR, et al. Atorvastatin for high-risk statin-naïve patients undergoing noncardiac surgery: The Lowering the Risk of Operative Complications Using Atorvastatin Loading Dose (LOAD) randomized trial. American heart journal. 2017;184:88-96

  Methods: We randomized 648 statin-naïve patients who were scheduled for noncardiac surgery and were at risk for a major vascular complication. Patients were randomized to a loading dose of atorvastatin or placebo (80 mg anytime within 18hours before surgery), followed by a maintenance dose of 40 mg (or placebo), started at least 12hours after the surgery, and then 40 mg/d (or placebo) for 7days. The primary outcome was a composite of all-cause mortality, nonfatal myocardial injury after noncardiac surgery, and stroke at 30days.

  Results: The primary outcome was observed in 54 (16.6%) of 326 patients in the atorvastatin group and 59 (18.7%) of 316 patients in the placebo group (hazard ratio [HR] 0.87, 95% CI 0.60-1.26, P=.46). No significant effect was observed on the 30-day secondary outcomes of all-cause mortality (4.3% vs 4.1%, respectively; HR 1.14, 95% CI 0.53-2.47, P=.74), nonfatal myocardial infarction (3.4% vs 4.4%, respectively; HR 0.76, 95% CI 0.35-1.68, P=.50), myocardial injury after noncardiac surgery (13.2% vs 16.5%; HR 0.79, 95% CI 0.53-1.19, P=.26), and stroke (0.9% vs 0%, P=.25).

  Conclusion: In contrast to the prior observational and trial data, the LOAD trial has neutral results and did not demonstrate a reduction in major cardiovascular complications after a short-term perioperative course of statin in statin-naïve patients undergoing noncardiac surgery. We demonstrated, however, that a large multicenter blinded perioperative statin trial for high-risk statin-naïve patients is feasible and should be done to definitely establish the efficacy and safety of statin in this patient population.

Appendix 3: Medline Search Strategy

[Database: Ovid MEDLINE(R) ALL <1946 to February 04, 2021>

Search Strategy:

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1 statins.mp. or Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (44334)

2 Ezetimibe, Simvastatin Drug Combination/ or Simvastatin/ or simvastatin.mp. (11241)

3 atorvastatin.mp. or Atorvastatin/ (10049)

4 rosuvastatin.mp. or Rosuvastatin Calcium/ (4025)

5 pitavastatin.mp. (1029)

6 lovastatin.mp. or Lovastatin/ (6013)

7 Fluvastatin/ (1402)

8 Pravastatin/ (3440)

9 Myocardial Infarction/ or Cardiovascular Diseases/ or cardiovascular events.mp. (338329)

10 cardiovascular mortality.mp. (14227)

11 stroke.mp. or Stroke/ (307809)

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (57745)

13 Percutaneous Coronary Intervention/ or major adverse cardiovascular events.mp. (23545)

14 9 or 10 or 11 or 13 (633526)

15 12 and 14 (14026)

16 limit 15 to (english language and full text and yr="2015 -Current" and (clinical trial, phase iii or comparative study or meta analysis or randomized controlled trial or "systematic review")) (266)

17 from 16 keep 6,9,18-19,23,25,29,54,82,87,102,106,114-115,120-121,130,133,139,164,170,180,221 (23)

Appendix 4: Key Inclusion Criteria

Population	**Patients with atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD**
Intervention	Statins or high intensive statin therapy
Comparator	Placebo or less intensive statin therapy
Outcomes	All-cause mortality, cardiovascular mortality, cardiovascular events (i.e. myocardial infarction, stroke, revascularization)
Timing	$\geq$ 1 year
Setting	Outpatient