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, February 3rd, 2022 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. Election of Chair and Vice-Chair	R. Citron (OSU)
	D. Approval of Agenda and Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
	F. Legislative Update	T. Douglass (OHA)
1:25 PM	II. CONSENT AGENDA TOPICS	(Chair)
	A. P&T Annual Report	
	B. P&T Operating Procedures	
	C. P&T Methods	
	D. Antipsychotics (Parenteral) Literature Scan	
	E. ACE Inhibitor/ARB/Direct Renin Inhibitor Focused Literature Scan	
	F. Oncology Prior Authorization Updates	
	1. Public Comment	
1:30 PM	III. DUR ACTIVITIES	
	A. Quarterly Utilization Report	R. Citron (OSU)
	B. ProDUR Report	L. Starkweather (Gainwell)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. Therapeutic Uses for Cannabinoids	
	2. Updates in Heart Failure Therapy	
1:45 PM	IV. DUR NEW BUSINESS	K. Sentena (OSU)
	A. Respiratory Syncytial Virus Policy Update	
	1. Synagis® (palivizumab) Literature Scan/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

V. PREFERRED DRUG LIST NEW BUSINESS

1:55 PM	A. Oral Antifungals Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Brexafemme® (ibrexafungerp citrate) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:10 PM	B. Pompe Disease Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Nexviazyme™ (avalglucosidase alfa-ngpt) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
2:30 PM	BREAK	
2:45 PM	C. Immunosuppressant Class Update with New Drug Evaluations 1. Class Update/Prior Authorization Criteria 2. Lupkynis™ (voclosporin) DERP report 3. Saphnelo™ (anifrolumab-fnia) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:15 PM	D. Oral Glucocorticoids Class Review 1. Class Review 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:45 PM	VI. EXECUTIVE SESSION	
4:30 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

Drug Use Research & Management Program
OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
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, 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, Dental3	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Vacant	Physician			December 2024

Drug Use Research & Management Program
OHA Health Systems Division
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, December 2nd, 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: Cathy Zehrung, RPh; Cat Livingston, MD; Stacy Ramirez, PharmD; Tim Langford, PharmD; Caryn Mickelson, PharmD; Robin Moody, MPH; William Origer, MD; Mark Helm, MD; Russell Huffman, PMHNP; Patrick DeMartino, MD

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Lan Starkweather, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Megan Herink, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Kathy Sentena, PharmD; Deborah Weston, JD

Audience: Becky Gonzales, ViiV Healthcare; Brandie Feger, Advanced Health; Donald Nopper, Apellis Pharmaceuticals; Edward Saito, Pacific University/Virginia Garcia; **Emily Smith, Zealand Pharma**; Haley Bruce, Artia Solutions; **Jamie Tobitt, Apellis Pharmaceuticals**; Jean Ritter, Zealand Pharma; Jeremy Strand, Alexion; Jody Legg; **Jonathan Frochtzwajg, Cascade AIDS project**; Katie Scheelar, EOCCO/Moda; Kelly Wright, Gilead Oncology; Laura Jeffcoat, Abbive; Mark Kantor, AllCare Health; Matt Worthy, OHSU; Matthew Ito, Regeneron; Melissa Snider; Michael Donabedian; Michael Foster, BMS; Olaf Reinwald, GBT; Rick Frees, Vertex Pharmaceuticals; Rob Perallon, Alexion; Roy Linfield, Sunovion; Shirley Quach, Novartis; **Sophia Yun, Janssen Scientific Affairs**; Stormy Cameron, Artia Solutions; **Stuart O'Brochta, Gilead**; Tanya Frost, Sites of Care; Tiina Andrews, Umpqua Health Alliance; Trent Taylor, JNJ; **Andrew Ahmann, OHSU; Maggi Olmon, AbbVie**

(*) Provided verbal testimony
Written testimony: Posted to OSU Website

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

I. CALL TO ORDER

A. Roll Call & Introductions
   - Called to order at approx. 1:05 p.m., introductions by staff and Committee
B. Approval of Agenda
C. Conflict of Interest Declaration – no new conflicts of interest were declared
D. Approval of August 2021 Minutes presented by Roger Citron
   ACTION: Motion to approve, 2nd, all in favor
E. Department Update provided by Trevor Douglass

II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization (PA) Updates
Recommendations:
- Add the following new FDA-approved antineoplastic agents to Table 1 in the Oncology Agents prior authorization (PA) criteria: Scemblix® (asciminib); Exkivity™ (mobecertinib); Tivdak™ (tisotumab vedotin-tftv)

B. Orphan Drug Policy Updates
Recommendations:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Tavneos™ (avacopan), Livmarli™ (maralixibat), and Bylvay™ (odevixibat) based on FDA-approved labeling

C. Inhaled Cystic Fibrosis Drugs Literature Scan
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Maintain inhaled mannitol as non-preferred
- Evaluate costs in executive session

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

III. DUR ACTIVITIES

A. **ProDUR Report**: Lan Starkweather, PharmD
B. **RetroDUR Report**: Dave Engen, PharmD
C. **Oregon State Drug Review**: Kathy Sentena, PharmD
   - **Covid-19 Vaccine Update**
   - **Deprescribing Techniques to Minimize Safety Issues Associated with Inappropriate Polypharmacy**

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

IV. DUR OLD BUSINESS

A. **Evkeeza™ (evinacumab-dgnb) Prior Authorization Update:** Megan Herink, PharmD
Recommendation:
- Update PA criteria to include renewal criteria
Public Comment: Matthew Ito, Regeneron
ACTION: The Committee recommended updating the PA criteria as proposed after amending to better assess clinical need by updating question #3 of the initial approval to require 12 weeks of maximally tolerated therapy. The Committee also recommended adding the proposed renewal PA criteria, but with an added question to evaluate pregnancy risk
Motion to approve, 2nd, All in favor

B. **Spravato® (esketamine) Safety Edit**: Sarah Servid, PharmD
Recommendation:
- Update the esketamine safety edit to clarify appropriate maintenance dose and use in patients with a history of substance use disorder
Public Comment: Sophia Yun, Janssen Scientific Affairs
ACTION: Motion to approve, 2nd, all in favor

V. DUR NEW BUSINESS

A. **HIV Pre-Exposure Prophylaxis Drug Use Evaluation**: Sarah Servid, PharmD
Recommendation:
- Develop an educational retrospective drug use review (DUR) program to improve provider knowledge of PrEP for patients with a recent STI, diagnosis of high-risk sexual behavior, or potential viral exposure
Public Comment: Jonathan Frochtzwajg, Cascade AIDS Project; Stuart O'Brochta, Gilead
ACTION: Motion to approve, 2nd, all in favor

VI. PREFERRED DRUG LIST NEW BUSINESS

A. **Glucagon Class Update with New Drug Evaluation (NDE)**: Kathy Sentena, PharmD
Recommendations:
- Make no changes to the PDL based on the review of recent clinical evidence
- Maintain dasiglucagon as non-preferred on the PDL
- Evaluate costs in executive session
Public Comment: Emily Smith, Zealand Pharma; Andrew Ahmann, OHSU
ACTION: Motion to approve, 2nd, all in favor

B. **Paroxysmal Nocturnal Hemoglobinuria (PNH) Class Update and NDE**:
Deanna Moretz, PharmD
Recommendations:
-Revise ravulizumab PA criteria to reflect expanded indication for use in pediatric patients aged 1 month and older with PNH or atypical hemolytic uremic syndrome
- Revise dosing (Table 1) to reflect updated indications
- Add pegcetacoplan to the "Biologics for Rare Diseases" drug class on the PDL
- Implement PA criteria for pegcetacoplan to limit use to FDA-approved indications funded by the OHP
- Evaluate costs in executive session
Public Comment: Jamie Tobitt, Apellis Pharma
ACTION: The Committee recommended implementing the proposed recommendations after adding a question to require providers assess for uncontrolled hypertension prior to initiation of therapy for applicable agents - including Aimovig®
Motion to approve, 2nd, all in favor

C. **Gonadotropin-Releasing Hormone (GnRH) Modifiers Class Update and NDE:**
Deanna Moretz, PharmD
Recommendations:
- Implement new PA criteria for GnRH modifiers to evaluate GnRH antagonists separately from GnRH agonists
- Evaluate costs in executive session
Public Comment: Maggi Olmon, AbbVie
ACTION: Motion to approve, 2nd, all in favor

D. **Growth Hormone Class Update and NDE**: David Engen, PharmD
Recommendations:
- Maintain lonapegsomatropin as non-preferred in the Growth Hormone PDL class
- Update PA criteria for GH agents to include lonapegsomatropin
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

E. **Bile Therapy Literature Scan and Prior Authorization Update**: Deanna Moretz, PharmD
Recommendations:
- Make no changes to the PDL based on the review of recent clinical evidence
- Modify obeticholic acid PA criteria to include recommended dosing parameters and safety precautions
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

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

VII. EXECUTIVE SESSION

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

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Lan Starkweather, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Megan Herink, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Kathy Sentena, PharmD; Deborah Weston, JD

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Inhaled Cystic Fibrosis Drugs Literature Scan**
Recommendation: Make tobramycin in sodium chloride (NaCl) nebulized solution preferred; Kitabis® Pak and its generic tobramycin nebulizer solution non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **Glucagon Class Update and NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

C. **Paroxysmal Nocturnal Hemoglobinuria (PNH) Class Update and NDE:**
Recommendation: Maintain pegcetacoplan as non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

D. **GnRH Modifiers Class Update and NDE**
Recommendation: Maintain relugolix/estradiol/norethindrone as non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

E. **Growth Hormone Class Update and NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

F. **Bile Therapy Lit Scan and PA Update**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: February 2022

MISSION:

To encourage safe, effective, and innovative drug policies that promote high value medications for patients served by the Oregon Health Plan (OHP) and other health care programs under the Oregon Health Authority (OHA) by evidence-based committee review of drug use research, clinical guidance and education.

DUTIES:

As defined by Oregon Revised Statutes (Chapter 414) the Pharmacy and Therapeutics (P&T) Committee was established to perform functions previously fulfilled by the Drug Use Review Board and Health Resources Commission. Responsibilities of the P&T committee include:

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.
4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs.
5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
6. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:
    a. Implementation of evidence-based algorithms.
    b. Any changes needed to any preferred drug list used by the authority.
    c. Practice guidelines for the treatment of mental health disorders with mental health drugs.
    d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.
7. Guide and approve meeting agendas.
8. Periodically review and update operating procedures and evidence grading methods as needed.

AD-HOC EXPERT INVOLVEMENT:

1. The Director shall appoint an ad hoc expert to the P&T Committee when:
    a. The P&T Committee determines it lacks current clinical or treatment expertise with respect to a particular therapeutic class; or
    b. An interested outside party requests appointment and demonstrates to the satisfaction of the Director that the P&T Committee lacks necessary clinical knowledge or treatment expertise with respect to a particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.

2. The medical experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of confidential pricing information or other conditions for the inclusion of a drug on the PDL. The medical experts may participate but may not vote in any other activities of the committee.

3. P&T staff also may engage relevant health care professionals with clinical specialty to serve as expert reviewers, in addition to the ad-hoc experts, if needed.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.
2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. Elections shall be held the first meeting of the calendar year.
3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.
4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.
5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug lists adopted by the OHA.
6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the OHA Director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.
7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.
    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

CONFLICT OF INTEREST POLICY:

The P&T Committee will function in a way that ensures the objectivity and credibility of its recommendations.

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc medical experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process which must be updated promptly with any changes in status.

2. Staff members are required to have no financial conflicts related to any pharmaceutical industry business for duration of work on P&T projects.

3. All disclosed conflicts will be considered before an offer of appointment is made.

4. If any material conflict of interest is not disclosed by a member of the P&T Committee on his or her application or prior to participation in consideration of an affected drug or drug class or other action of the Committee, that person will not be able to participate in voting decisions of the affected drug or drug class and may be subject to dismissal. Circumstances in which conflicts of interest not fully disclosed for peer reviewers, ad-hoc experts, or persons providing public comment will be addressed on a case by case basis.

5. Any person providing public testimony will also be required to disclose all conflicts of interest including, but not limited to, industry funded research prior to any testimony pertaining to issues before the P&T Committee. This includes any relationships or activities which could be perceived to have influenced, or that would give the appearance of potentially influencing testimony.

PUBLIC COMMENT:

1. The P&T Committee meetings will be open to the public

2. The P&T Committee shall provide appropriate opportunity for public testimony at each meeting

    a. Testimony can be submitted in writing or provided in-person. Persons planning to provide oral testimony during the meeting must sign up and submit a conflict of interest form no later than 24 hours prior to the start of the meeting.

    b. Maximum of 3 minutes per speaker/institution per agenda item

        i. Information that is most helpful to the Committee is evidence-based and comparative research, limited to new information not already being reviewed by the Committee.
        ii. Oral presentation of information from FDA-approved labeling (i.e., Prescribing Information or "package insert") is not helpful to the Committee.

    c. Written testimony can be submitted by interested parties for the P&T Committee to consider on agenda items. Written testimony that includes clinical information should be submitted for evaluation by staff at least 2 weeks prior to the scheduled meeting through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

d. Written documents provided during scheduled public testimony time of P&T Committee meetings will be limited to 2 pages of new information that was not included in previous reviews. Prescribing Information is not considered new information; only clinically relevant changes made to Prescribing Information should be submitted.

e. If committee members have additional questions or request input from public members during deliberations after the public comment period, members of the public may be recognized at the discretion of the committee chair to answer questions of the committee or provide additional commentary.

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the PDL and clinical prior authorization criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices. For detailed description of review standards, preferred sources of evidence, and evidence grading methods, see Quality Assessment Tool and Evidence Grading Methods.

2. Final documents as outlined in Chapter 414 of the Oregon Revised Statutes shall be made publicly available at least 30 days prior to review by the P&T Committee. Written public comments submitted during the draft comment period prior to posting of final documents are only considered by staff. Written public comment submitted based on final documents will be submitted to the P&T Committee for consideration. Posted documents will include the agenda for the meeting, a list of drug classes to be considered, and background materials and supporting documentation which have been provided to committee members with respect to drugs and drug classes that are before the committee for review.

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

    a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

    b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.
        i. Until new drugs are reviewed by the P&T Committee, drugs meeting the following criteria will be reviewed to ensure they are used appropriately for an FDA-approved or compendia-supported indication, with FDA-approved dosing, and that the indication is funded by the OHP:
            a. A new drug in a drug class with clinical prior authorization criteria.
            b. A new drug used for a non-funded condition on the HERC Prioritized List of Health Services.

c. A new drug not in a PDL class with existing PA criteria identified by the reviewing pharmacist during the weekly claim processing drug file load costing more than $5,000 per claim or $5,000 per month.

c. Line Extension and Combination Product Policy
    i. Line extensions include new strengths or new formulations of an existing drug.
        1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
        2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
    ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
    iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

    a. Literature of drug classes that have previously been reviewed for the PDL will be scanned and evaluated as needed to assess the need to update drug policies based on clinically relevant information and significant changes in costs published since the last review.
    b. Abbreviated drug reviews will evaluate drugs for unfunded conditions. Evidence supporting these reports is derived primarily from information in the product labeling.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Review Standards and Methods for Quality Assessment of Evidence
Updated: February 2022

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the preferred drug list (PDL) and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

2. The types of reviews may include, but are not limited to, the following:

Type of Review	Rationale for Review
Abbreviated Drug Review	New drug with evidence only for non-funded condition(s)
Class Literature Scan	Used when limited literature is found which would affect clinical changes in PDL status or PA criteria based on efficacy or safety data (may include new drug formulations or expanded indications if available literature would not change PDL status or PA criteria). Provides a summary of new or available literature, and outcomes are not evaluated via the GRADE methodology listed in **Appendix D**.
New Drug Evaluation (NDE)	Single new drug identified and the PDL class was recently reviewed, or the drug is not assigned to a PDL drug class
Class Review	New PDL class
Class Update	New systematic review(s) and clinical trials identified that may inform change in PDL status or clinical PA criteria in an established PDL class
Class Update with New Drug Evaluation	New drugs(s) or indication(s) also identified (excludes new formulations, expanded indications, biosimilars, or drugs for unfunded indications)
DERP Summary Report	New DERP report which evaluates comparative evidence
Drug Use Evaluation	Analysis of utilization trends in FFS population in order to identify safety issues or inform future policy decisions
Policy Evaluation	Evaluation safety, efficacy, and utilization trends after implementation of a policy to identify areas for improvement

3. The P&T Committee will rely primarily on high quality systematic reviews and randomized controlled trials in making its evidence summary recommendations. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence.

4. Emphasis will be placed on the highest quality evidence available. Poor quality trials, systematic reviews or guidelines are excluded if higher quality literature is available and results offer no additional value. Unless the trial evaluates an outcome or comparison of high clinical importance, individual RCTs with the following study types will be excluded from class updates, class reviews, and literature scans:
    a. Non-comparative, placebo-controlled trials
    b. Non-inferiority trials
    c. Extension studies
    d. Poor quality studies (as assessed in **Appendix A**)

5. Individual drug evaluations rely primarily on high quality RCTs or clinical trials used for FDA approval. Evidence from poor quality RCTs may be included if there is no higher quality evidence available.

6. The following are preferred sources that provide high quality evidence at this time:

    a. Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    f. BMJ Clinical Evidence

7. The following types of evidence are preferred and will be considered only if they are of high methodological quality as evaluated by the quality assessment criteria below:

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

8. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

    a. Observational studies, case reports, case series
        i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents

c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
d. Studies not designed to investigate clinically relevant outcomes
e. Systematic reviews identified with the following characteristics:
    i. Evidence is of poor or very poor quality
    ii. Evidence is of limited applicability to a US population
    iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
    iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
    v. Evidence is based on indirect comparisons from network meta-analyses
    vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
f. Guidelines identified with the following characteristics:
    i. There is no systematic guideline development method described
    ii. Strength of evidence for guideline recommendations are not provided
    iii. Recommendations are largely based on expert opinion
    iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
    v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

QUALITY ASSESSMENT

1. The standard methods used by the DURM faculty to assess quality of evidence incorporated into the evidence summaries for the OHP Pharmacy and Therapeutics Committee are described in detail in **Appendix A-C**.

2. The Cochrane Risk of Bias tool (modified) described in **Appendix A** is used to assess risk of bias (i.e., internal validity) of randomized controlled trials. The quality of non-inferiority trials will be also assessed using the additional criteria for non-inferiority trials in **Appendix A**. Internal validity of clinical trials are graded as poor, fair, or good quality.

3. The AMSTAR II measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Systematic reviews, meta-analyses or guidance identified from 'best sources' listed in **Appendix B** undergo methodological rigor and are considered to be high quality and are not scored for quality using the AMSTAR II tool.

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**. If there are concerns regarding applicability of guidelines to the Medicaid population, the AGREE-REX tool is available for use (https://www.agreetrust.org/resource-centre/agree-rex-recommendation-excellence/).

5. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability, or directness, of randomized controlled trials to the OHP population. Detailed guidance is provided in **Appendix A**. Only randomized controlled trials with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries.

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

7. The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm using the GRADE methodology listed in **Appendix D**. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient**. Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
        iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
        iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

8. Conflict of Interest
    a. Conflict of interest is a critical component of quality assessment. A conflict of interest is "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a second interest." Conflict of interest includes any relationships or activities that could be perceived to have influenced or give the appearance of potentially influencing the literature.
        i. Reference: IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice.* Washington, DC: The National Academies Press.

    b. Conflict of interest analysis for DURM reviews:
        1. Sources will be excluded due to conflict of interest concerns if they contain one of the "fatal flaws" in **Table 1** below.
        2. If no "fatal flaws" exist, an analysis of the conflicts of interest will be completed and any limitations (examples in **Table 1** below) will be first and foremost discussed in the evidence review.
        3. Conflict of interest is also assessed through the Cochrane risk of bias, AMSTAR II, and AGREE tools (**Appendix A, B, and C**).

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented • Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies
Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion		• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Reporting bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).
Other Bias	Other sources of bias may be present depending on conflict of interests and funding sources, trial design, or other specific circumstances not covered in the categories above. Of particular concern is how conflicts of interest and funding sources may potentially bias results. Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. Information about vested interests should be collected and presented when relevant, with specific regard for methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. Additional sources of bias may result from trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get 'mixed', for example if participants pool their drugs).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Conflicts of interest should also be assessed when determining risk of bias. This may be considered part of risk of reporting bias. Funding sources for the trial, conflicts of interest of the authors, and role the study sponsor played in the trial should be considered in this domain.

The quality of each trial will be graded as **good, fair,** or **poor** based on the following thresholds for converting the Cochrane Risk of Bias Tool to AHRQ Standards. A good quality trial will have low risk of bias for all domains. A fair quality trial will have one domain with high risk of bias or 2 domains with unclear bias, with the assessment that the one or more biases are unlikely to influence the outcome, and there are no known limitations which could invalidate results. A poor quality trial will have high risk of bias for one or more domains or have 2 criteria with unknown bias for which there may be important limitations which could invalidate the results or likely bias the outcome. Trials of poor quality will be excluded from review if higher quality sources of evidence are available

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Systematic differences in how care was provided between groups due to un-blinding of participants or investigators/care providers or because of standard of care was not consistent across all sites.	• Study participants could not identify study assignment because blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Study participants could possibly identify study assignment because there was no blinding or incomplete blinding • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups)	Not described or insufficient information to permit definitive judgment

		• Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	
DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	• Outcome data assessors could possibly identify study assignment because no blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, large differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest	Insufficient information to make determination

		• Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	
OTHER BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of other biases not described in the categories above	• No conflicts of interest present or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest are present based on funding source or conflicting interests of authors • Study sponsor is involved in trial design, data analysis, and publication of data • There is a run-in period with pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention • Recruitment bias in cluster-randomized trials with differential participant recruitment in clusters for different interventions • Cross-over trials in which the crossover design is not suitable, there is significant carry-over effects, or incompletely reported data (data reported only for first period) • Conduct of the study is affected by interim results ((e.g. recruiting additional participants from a subgroup showing more benefit) • Deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).	• Conflicts of interest for authors or funding sources are not reported or not described • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Non-inferiority (NI) trials are designed to prove a new treatment is not worse than the control treatment by a pre-determined difference, with a given degree of confidence. The pre-determined margin of difference in non-inferiority trials is defined as delta. Correctly determining this margin is a challenge in the design and interpretation of NI trials. The greatest challenge in use of NI trials is recognizing inappropriate use.

Non-inferiority trials will only be included in evidence summaries when there is a compelling reason to include them, and higher quality evidence is not available. The compelling reason for inclusion will be clearly stated as an introduction to the reporting of the NI trial.

The following template was developed using CONSORT and FDA guidance[1,2] and will be used as a guideline to evaluate non-inferiority studies included in DURM evidence summaries. Unless the trial evaluates an outcome or comparison of high clinical importance, individual non-inferiority trials will be excluded from class updates, class reviews, and literature scans. Evidence from poor quality RCTs may be included in individual drug evaluations if there is no higher quality evidence available. Items in bold (#1-5) are essential to conducting a non-inferiority trial with good methodological rigor. In general, a non-inferiority trial with high quality methods will score a "yes" on most of the components listed below.

Table 4. Non-inferiority Trial Quality Scoring Template

Developed using CONSORT and FDA guidance[1,2] **Use Template to evaluate trials supporting New Drug Evaluations and Class Update Reports** **A high-quality trial will meet all bolded assessments below**	
1. Rationale for choosing comparator with historical study results confirming efficacy (or safety) of this comparator is provided.	□ **Yes** □ **No** □ **Can't answer**
2. Active control (or comparator) represents current standard of care.	□ **Yes** □ **No** □ **Can't answer**
3. Non-inferiority margin was specified a priori and based on statistical reasoning and clinical considerations regarding benefit, risk, and cost.	□ **Yes** □ **No** □ **Can't answer**
4. Noninferiority margin is not larger than the expected difference between active control (or comparator) and placebo.	□ **Yes** □ **No** □ **Can't answer**
5. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, the justification for switching is provided and superiority analysis was defined a priori.	□ **Yes** □ **No** □ **Can't answer**
6. Investigator reported both ITT and per-protocol analysis in detail and the results of both analyses demonstrate noninferiority. (If only one analysis is provided, per protocol is subject to less bias than ITT analysis in noninferiority trials.)	□ **Yes** □ **No** □ **Can't answer**
7. Rationale for using a noninferiority design is included (or why it would likely be unethical to conduct a placebo-controlled superiority trial of the new therapy).	□ Yes □ No □ Can't answer
8. Study hypothesis is stated in terms of noninferiority.	□ Yes □ No □ Can't answer
9.Eligibility criteria for participants and the settings in which the data were collected are similar to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
10. Trial is designed to be consistent with historical placebo-controlled trials.	□ Yes □ No □ Can't answer
11. The reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy (or safety).	□ Yes □ No □ Can't answer
12. The outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
13. The lower bound of that CI is clinically significant.	□ Yes □ No □ Can't answer
14. For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin is included.	□ Yes □ No □ Can't answer
15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:
1. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *Jama.* 2012;308(24):2594-2604.
2. FDA Industry Guidance for Noninferiority Trials. November 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the measurement tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies were not assessed or considered when conclusions were formulated (#9 and #13)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); National Institute for Health and Care Excellence (NICE); U.S. Department of Veterans Affairs (VA); and Canadian Agency for Drugs and Technologies in Health (CADTH); and BMJ Clinical Evidence.

AMSTAR II Quality Scoring Template			
1)	**Did the research questions and inclusion criteria for the review include the components of PICO?**		
	For Yes:		□ Yes
	□ Population	Optional (recommended)	□ No
	□ Intervention	□ Timeframe for follow-up	
	□ Comparator group		
	□ Outcome		
2)	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**		
	For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:	**For Yes:** As for partial yes, plus the protocol should be registered and should also have specified:	□ Yes □ Partial Yes
	□ review question(s)	□ a meta-analysis/synthesis plan, if appropriate, and	□ No
	□ a search strategy	□ a plan for investigating causes of heterogeneity	
	□ inclusion/exclusion criteria	□ justification for any deviations from the protocol	
	□ a risk of bias assessment		
3)	**Did the review authors explain their selection of the study designs for inclusion in the review?**		
	For Yes, the review should satisfy ONE of the following:		□ Yes
	□ Explanation for including only RCTs		□ No
	□ OR Explanation for including only NRSI		
	□ OR Explanation for including both RCTs and NRSI		

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from:
- unconcealed allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- from confounding, and
- from selection bias

For Yes, must also have assessed RoB:
- methods used to ascertain exposures and outcomes, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10) Did the review authors report on the sources of funding for the studies included in the review?

For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- Yes
- No

11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

- Yes
- No
- No meta-analysis conducted

NRSI	**For Yes:** □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	□ Yes □ No □ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** **For Yes:** □ included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	□ Yes □ No □ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** **For Yes:** □ included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	□ Yes □ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** **For Yes:** □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	□ Yes □ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	□ Yes □ No □ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest	□ Yes □ No

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The AGREE II is an updated instrument that has been validated. It consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated global rating scale (GRS) was developed, and is generally a reasonable alternative to AGREE II if resources are limited. The AGREE II-GRS instrument consists of only 4 items (**Table 2**). As the AGREE II-GRS does not take into account conflicts of interest, questions 22 and 23 regarding "Editorial Independence" will also be evaluated in conjunction with the AGREE II-GRS. With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II and each component of the AGREE II-GRS.

Table 1. AGREE II Instrument.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**

9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**
11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. AGREE II Global Rating Scale (modified).

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.
5	The views of the funding body have not influenced the content of the guideline. **[SCORE:]**	• Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
6	Competing interests of guideline development group members have been recorded and addressed. **[SCORE:]**	• There should be an explicit statement that all group members have declared whether they have any competing interests. • All competing interests should be listed • There should be no significant competing interests

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:

- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

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

Drug Class Literature Scan: Antipsychotics, Parenteral

Date of Review: February 2022

Date of Last Review: August 2020
Literature Search: 03/12/20 – 11/30/2021

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

Conclusions:

- Since the last Pharmacy and Committee review, 1 systematic review[1] and 2 guidelines[2,3] have been published.
- The objective of a Cochrane systematic review published in August 2020 was to review the effects of maintaining antipsychotic drugs for people with schizophrenia compared to withdrawing these agents.[1] Any antipsychotic dose or mode of administration (oral or by injection) was included in the search strategy. When all eligible studies were combined, antipsychotic drugs were more effective than placebo at preventing relapse (drug 22% versus placebo 58%, 71 randomized controlled trials [RCTs], n=8666, risk ratio [RR] 0.35, 95% confidence interval [CI] 0.30 to 0.40, number needed to obtain beneficial outcome [NNTB] 3).[1] Antipsychotic drugs were associated with more participants experiencing movement disorders (drug 14% versus placebo 8%, 29 RCTs, n = 5276, RR 1.52, 95% CI 1.25 to 1.85, number needed to treat for an additional harmful outcome [NNTH] 20), sedation (drug 8% versus placebo 5%, 18 RCTs, n=4078, RR 1.52, 95% CI 1.24 to 1.86, NNTH 50), and weight gain (drug 9% versus placebo 6%, 19 RCTs, n=4767, RR 1.69, 95% CI 1.21 to 2.35, NNTH 25).[1]
- In November 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a review of extended-release (ER) injectable risperidone (PERSERIS).[2] The primary outcome was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score after 8 weeks of treatment.[4] A 20% improvement in the PANSS total score is considered a clinical meaningful response to treatment in schizophrenia patients.[5] The PANSS total score change for participants receiving ER risperidone 90 mg, ER risperidone 120 mg, and placebo was reported as a least squares mean [LSM] of −15.37, −16.46 , and −9.22 respectively.[2] Compared with placebo, both ER risperidone doses demonstrated statistically significant improvements in the PANSS score (ER risperidone 90 mg versus placebo: least squares mean difference [LSMD] of −6.15, 95% CI, −9.98 to −2.31; P=0.0004 and ER risperidone 120 mg versus placebo: LSMD −7.24, 95% CI, −11.05 to −3.43; P<0.0001).[2] However, a 20% improvement in PANSS score was not achieved for either ER risperidone dose.[2] The proportion of the patients who experienced at least 1 treatment-emergent adverse event (TEAE) was reportedly higher for the ER risperidone 120 mg group (77.8%) compared with the ER risperidone 90 mg (70.4%) and placebo groups (68.6%).[2]
- The American Psychiatric Association (APA) updated guidance for the treatment of patients of schizophrenia in 2021.[3] The APA recommends patients receive treatment with a long-acting injectable (LAI) antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence (Strong Recommendation, Moderate-Quality Evidence).[3] Dosing recommendations for LAI antipsychotics included in the APA 2021 guidance are presented in **Table 1**.

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- No changes to the Preferred Drug List (PDL) are recommended.
- Review costs in Executive Session.

Summary of Prior Reviews and Current Policy

Evidence for the comparative effectiveness of first-generation antipsychotics, second-generation antipsychotics, and parenteral antipsychotic products was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in August 2020. The efficacy and safety of lumateperone, an oral second-generation antipsychotic which received Food and Drug Administration (FDA) approval in 2019 for treatment of adults with schizophrenia, was also reviewed at this meeting.

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and prior authorization (PA) requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. The parenteral antipsychotics included on the Oregon PDL are presented in **Appendix 1.** Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and trifluoperazine are preferred on the Preferred Drug List. During the second quarter of 2021, the majority of antipsychotic use in the Oregon Medicaid population was for oral second generation antipsychotics including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 5% of antipsychotic medication claims were for parenteral formulations. Paliperidone, aripiprazole, and haloperidol decanoate are the most frequently prescribed injectable agents in this class.

Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms for schizophrenia, bipolar mania or major depressive disorder (MDD) and that there is insufficient evidence to determine if new formulations of LAI aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan 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 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 Food and Drug Administration (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:

<u>Cochrane Collaborative</u>

The objective of a Cochrane systematic review published in August 2020 was to review the effects of maintaining antipsychotic drug therapy for people with schizophrenia compared to withdrawing these agents.[1] This was an update of a previous Cochrane review published in 2012. Literature was searched through September 2019. Any antipsychotic dose or mode of administration (oral or by injection) was included in the search strategy. The primary outcome of interest was relapse at 1 year as defined by the original studies or by a deterioration in mental state requiring further treatment.[1] Overall, 75 studies involving 9,145

participants met inclusion criteria.[1] Of the included studies, 17 had a duration up to three months.[1] Twenty-six studies lasted up to 6 months and 25 studies up to 12 months.[1] Seven studies lasted more than 12 months.[1] The longest study had a duration of 3 years.[1] Twenty-nine studies were conducted in hospitals (at least at the start of the trial) and 34 studies in outpatients.[1] Seven studies included both inpatients and outpatients.[1] Seventy-three studies compared maintenance treatment with antipsychotic drugs and inactive placebo; two open-label RCTs compared antipsychotic drugs with no treatment.[1] No data on active placebo as a comparator were available.[1] Relapse definition varied between studies. The main relapse criteria in 25 studies was clinical judgement,[1] while 24 studies used various rating-scale-based definitions, 16 studies defined relapse as need of medication, 4 studies defined relapse as admission to hospital, 2 studies described relapse as dropout due to worsening of symptoms, and 4 studies did not indicate the criteria for relapse.[1] Most studies had either a neutral sponsor or sponsorship was not indicated.[1] Twenty-five studies were industry sponsored.[1] In many studies the methods of randomization, allocation and blinding were poorly reported.[1] Most trials had an unclear risk of bias.[1]

When all eligible studies were combined, antipsychotic drugs were more effective than placebo at preventing relapse (drug 22% versus placebo 58%, 71 RCTs, n=8666, RR 0.35, 95% CI 0.30 to 0.40, NNTB 3, 95% CI 2 to 3).[1] The outcomes were analyzed for different lengths of follow-up: up to 3 months, 4 to 6 months, 7 to 12 months, and more than one year. Antipsychotic medication was more effective than placebo in preventing relapse in studies lasting up to 3 months (percentage of participants who relapsed despite receiving antipsychotic medication was 12% compared with 35% of participants who received placebo and relapsed, 44 RCTs, n=6362, RR 0.34, 95% CI 0.28 to 0.40, NNTB 4, 95% CI 3 to 5).[1] These results were also seen in studies lasting 4 to 6 months (drug 18% versus placebo 49%, 49 RCTs, n=7599, RR 0.36, 95% CI 0.31 to 0.42, NNTB 3, 95% CI 3 to 4).[1] High certainty evidence was provided in studies lasting 7 to 12 months (primary outcome: drug 24% versus placebo 61%, 30 RCTs, n=4249, RR 0.38, 95% CI 0.32 to 0.45, NNTB 3) and more than 12 months (drug 31% versus placebo 68%, 10 RCTs, n=1786, RR 0.46, 95% CI 0.33 to 0.64, NNTB 3).[1]

Antipsychotic drug use (as a group and irrespective of duration) was associated with more participants experiencing movement disorders (e.g. at least one movement disorder: drug 14% versus placebo 8%, 29 RCTs, n=5276, RR 1.52, 95% CI 1.25 to 1.85, NNTH 20), sedation (drug 8% versus placebo 5%, 18 RCTs, n=4078, RR 1.52, 95% CI 1.24 to 1.86, NNTH 50), and weight gain (drug 9% versus placebo 6%, 19 RCTs, n=4767, RR 1.69, 95% CI 1.21 to 2.35, NNTH 25).[1] For people with schizophrenia, the evidence suggests that maintenance on antipsychotic drugs prevents relapse to a much greater extent than placebo for approximately up to two years of follow-up.[1] This effect must be weighed against the adverse effects of antipsychotic drugs.[1]

After review, 2 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[6,7]

New Guidelines:

High Quality Guidelines:

<u>Canadian Agency for Drugs and Technologies in Health</u>

In November 2021 CADTH published a review of ER injectable risperidone (PERSERIS).[2] Extended-release risperidone subcutaneous (SC) injection was approved by Health Canada in November 2020[2] and by the FDA in July 2018.[8] It is indicated for the treatment of schizophrenia in adults.[8] The recommended dose is 90 mg or 120 mg once monthly by SC injection.[8] Extended-release subcutaneous risperidone does not require a loading dose or supplementation with oral risperidone.[8] Extended-release risperidone 90 mg injection corresponds to 3 mg per day oral risperidone, and ER risperidone 120 mg injection corresponds to 4 mg per day oral risperidone.[8]

One phase 3, randomized, double-blind, placebo-controlled study that was performed at 33 sites in the United States was included in the summary of the CADTH clinical evidence.[4] The objective of the RCT was to evaluate the efficacy and safety of ER risperidone compared with placebo in patients (n=354) aged 18 to 55 years with moderate-to-severe schizophrenia in an acute exacerbation phase.[4] Participants could be either receiving treatment or not receiving treatment for schizophrenia. At the first visit, all participants received 0.25mg oral risperidone for 2 days to assess medication tolerability. If they were receiving antipsychotic medication, they were admitted into an inpatient setting and tapered off their current oral antipsychotic medication over 3 to 8 days. Patients were randomized to 1 of 3 treatment groups: ER risperidone 90 mg SC, ER risperidone 120 mg SC, or placebo injection SC for 8 weeks.[4] The primary outcome was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at end-of-treatment. The secondary outcome was change from baseline to end of treatment on the Clinical Global Impression–Severity of Illness (CGI-S). [2] The majority of patients included in the study were Black (> 70%) and male (> 73.5%).[2] The mean age ranged from 40.5 to 42.4 years across the 3 groups.[2]

The PANSS total score change from baseline for participants receiving ER risperidone 90 mg, ER risperidone 120 mg, and placebo was reported as a least squares mean [LSM] of −19.86, −23.61, and −13.37 respectively.[8] A 20% improvement in the PANSS total score is considered a clinical meaningful response to treatment in schizophrenia patients.[5] Compared with placebo, both ER risperidone doses demonstrated statistically significant improvements in PANSS score from baseline (ER risperidone 90 mg vs. placebo: LSMD −6.15, 95% CI, −9.98 to −2.13; P=0.0004 and ER risperidone 120 mg vs placebo: LSMD −7.24, 95% CI, −11.045 to −3.43; P<0.0001).[4] It is uncertain whether the difference between the ER risperidone treatment groups and placebo group was clinically meaningful, as a 20% improvement in PANSS score was not achieved.[8]

In terms of change from baseline in CGI-S score, all 3 groups demonstrated a change at Day 57 (LSM of −0.87, −0.91, and −0.52 in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] Compared with placebo, both ER risperidone doses demonstrated a statistically significant improvement in CGI-S score (LSMD −0.35, 95% CI, −0.56 to −0.14; P = 0.0002 for risperidone ER 90 mg versus placebo and LSMD −0.40, 95% CI, −0.60 to −0.19; P < 0.0001 for risperidone ER 120 mg versus placebo).[4] However, neither the change from baseline for either ER risperidone treatment group, nor the treatment group difference between the ER risperidone groups and placebo, met the minimal important difference (i.e., a reduction of 1 point in the CGI-S).[2] Therefore, the clinical significance of the observed findings in CGI-S score changes is unclear.[2]

The proportion of the patients who experienced at least 1 TEAE was reportedly higher for the ER risperidone 120 mg group (77.8%) compared with the ER risperidone 90 mg (70.4%) and placebo groups (68.6%).[2] Overall, the most frequently reported TEAEs that occurred at higher rates in the ER risperidone groups compared with the placebo group were weight gain (13%, 12.8%, and 3.4% in the ER risperidone 90 mg and 120 mg groups and the placebo group, respectively) and somnolence (5.2%, 4.3%, and 0% in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] There were no deaths reported during the treatment periods.[2] The incidence of serious TEAEs was infrequent (0%, 0.9%, and 0.8% in the ER risperidone 90 mg and 120 mg groups and the placebo group, respectively).[2] The proportion of patients who withdrew due to adverse events (AEs) was reportedly low (0%, 1.7%, and 2.5% in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] Regarding the AEs of special interest, more patients (13%) in the ER risperidone groups experienced weight gain compared with patients who received placebo (3.4%), which was an expected AE that has been reported in all other atypical antipsychotic drugs.[2]

The 8-week duration of the double-blind randomized controlled trial was considered short to assess the long-term maintenance effect of treatment.[2] There was no direct or indirect treatment comparison evidence to compare ER risperidone with oral risperidone or risperidone LAI (IM every 2 weeks) or other relevant atypical antipsychotic LAIs currently marketed in Canada.[2] Based on the summary of clinical evidence, ER risperidone 90 mg and 120 mg (SC once monthly) showed statistically significant improvements in schizophrenia symptoms compared with placebo after 8 weeks, as measured by PANSS total scores and CGI-S scores; however, given that improvements in these outcomes were also observed in the placebo group, the clinical importance of these results is uncertain.[2] The

safety of the once-monthly formulation appears to be consistent with the safety profile of risperidone (both oral and LAI every 2 weeks).[2] Key evidence gaps include the short duration of the trial; ER risperidone is intended to be used as a chronic treatment and longer trials comparing it with the existing oral risperidone or LAI atypical antipsychotic drugs available in Canada for the maintenance treatment of schizophrenia are needed to adequately assess the long-term outcomes, including mortality, relapse, remission, and hospitalization.[2]

The CADTH recommendations state adult patients with well-diagnosed schizophrenia or schizoaffective disorder who have responded to oral risperidone are candidates for ER risperidone SC injection.[2] Geriatric and pediatric patients are not good candidates for risperidone, given the lack of data on these groups and the risk of stroke and increased mortality in older adults.[2] In addition, patients with appropriately diagnosed treatment-resistant illness are unlikely to benefit.[2] Risperidone ER has not undergone adequate study in pregnant patients to determine whether it is safe, especially in the first trimester of pregnancy.[2] The benefits may outweigh the risks of ER risperidone ER for certain patients, and close monitoring would be necessary if it is prescribed to a pregnant patient.[2]

American Psychiatric Association

The APA published updated guidance for the treatment of patients of schizophrenia in 2021.[3] Since publication of the last APA practice guideline in 2004 and guideline watch on schizophrenia in 2009, there have been many studies on new pharmacological and nonpharmacological treatments for schizophrenia.[3] The updated guidance was based on an AHRQ systematic review completed in 2017.[9] The APA recommends patients receive treatment with a LAI antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence (Strong Recommendation, Moderate-Quality Evidence).[3] Dosing recommendations for LAI antipsychotics included in the APA 2021 guidance are presented in **Table 1**.

Long acting injectable formulations of antipsychotic medications can provide a number of benefits for patients, families, and clinicians, yet they are often underutilized.[3] Racial differences also exist in the proportion of individuals who are treated with LAI antipsychotic medications, with greater use of these formulations in Black patients than in White patients.[3] Presumably due to improved adherence, advantages of LAI antipsychotics include the potential for a decreased risk of mortality, reduced risk of hospitalization, and decreased rates of treatment discontinuation.[3] Other benefits for patients include a subjective sense of better symptom control, greater convenience as a result of needing to take fewer medications daily, and reduced conflict with family members or other persons of support related to medication-related reminders.[3] Although some patients may not wish to experience the discomfort associated with receiving injections of medications, this is not a major barrier for most patients.[3] In addition, discomfort can often be minimized by using second generation LAIs rather than first generation LAIs, which have sesame oil based vehicles, or by using an LAI with a small injection volume or lower administration frequency.[3]

Table 1. Long-acting injectable antipsychotic medications[3]

Generic Name	Brand Name	Maintenance Dose	Frequency	Need for Initial Oral Supplementation
First-generation Agents				
Fluphenazine	PROLIXIN DECANOATE	12.5 mg to 50 mg IM	Every 2-4 weeks	Decrease oral dose by half after first injection, then discontinue with second injection
Haloperidol	HALDOL DECANOATE	50 mg to 450 mg IM	Every 4 weeks	Taper and discontinue after 2 to 3 injections
Second-generation Agents				
Aripiprazole monohydrate	ABILIFY MAINTENA	200 mg to 400 mg IM	Every 4 weeks	Continue oral dose for 14 days after initial injection

Aripiprazole lauroxil	ARISTADA INITIO	675 mg IM	Single initiation dose: not for repeated dosing	Must be administered in conjunction with aripiprazole 30mg oral dose
Aripiprazole lauroxil	ARISTADA	441 mg to 1,064 mg IM	• 441, 662, or 882 mg every 4 weeks • 882 mg every 6 weeks • 1,064 mg every 8 weeks	Give 21 days of stabilized oral aripiprazole in conjunction with Aristada injection. (Conversion of oral aripiprazole to IM aripiprazole is based on current oral aripiprazole dose.)
Olanzapine	ZYPREXA RELPREVV	150 mg to 405 mg	• 300 mg every 2 weeks • 405 mg every 4 weeks	Not required
Paliperidone palmitate	INVEGA SUSTENNA	78 mg to 234 mg IM	Every 4 weeks	Not required
Paliperidone palmitate	INVEGA TRINZA	273 mg to 819 mg	Every 12 weeks	Not applicable: change to Trinza after at least 4 maintenance doses of Sustenna
Risperidone	RISPERDAL CONSTA	25 mg to 50 mg IM	Every 2 weeks	Continue oral risperidone for 3 weeks
Risperidone	PERSERIS	90 mg to 120 mg SC	Every 4 weeks	Not required
Abbreviations: IM = intramuscular; mg = milligram; SC = subcutaneous				

After review, no guidelines were excluded due to poor quality.

New Formulations:
Paliperidone palmitate (INVEGA HAFYERA) received FDA approval August 2021. This new formulation of extended-release paliperidone intramuscular injection is administered by a healthcare professional via gluteal injection every 6 months.[10] The dose of INVEGA HAFYERA ranges from 1,092 mg to 1,560 mg depending on the prior maintenance dose of INVEGA SUSTENNA (156 mg or 234 mg) or INVEGA TRINZA (546 or 819 mg).[10] Switching to INVEGA HAFYERA from other doses of INVEGA SUSTENNA (39 mg, 78 mg, and 117 mg) or INVEGA TRINZA (273 mg and 410 mg) has not been studied.[10] INVEGA HAFYERA is indicated for the treatment of schizophrenia in adults after they have been adequately treated with either:

- once-a-month paliperidone palmitate extended-release injectable suspension (INVEGA SUSTENNA) for at least 4 months or
- every-three-month paliperidone palmitate extended-release injectable suspension (INVEGA TRINZA) for at least one 3 month-cycle.[10]

The safety and efficacy of INVEGA HAFYERA were evaluated in a non-inferiority, double-blind RCT which compared INVEGA HAFYERA administered every 6 months with INVEGA TRINZA administered every 3 months over a 12 month period.[10] Patients in the INVEGA HAFYERA arm received placebo injections at every other 3 month visit to maintain blinding. All participants with schizophrenia had previously been stably treated for at least 4 months with INVEGA SUSTENNA or at least one 3-month injection cycle with INVEGA TRINZA.[10] The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥25% increase (if the baseline score was >40) or a 10-point increase (if the baseline score was ≤40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation: a score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.[10] A relapse event was experienced by 7.5%

and 4.9% of patients in the INVEGA HAFYERA and INVEGA TRINZA treatment groups, respectively, with the Kaplan-Meier estimated difference between INVEGA HAFYERA and INVEGA TRINZA of 2.9% (95% CI -1.1 to 6.8).[10] The upper bound of the 95% CI (6.8%) was less than 10%, the prespecified non-inferiority margin.[10] The study demonstrated non-inferiority of INVEGA HAFYERA to INVEGA TRINZA. An evaluation of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.[10]

The injection volume of INVEGA HAFYERA ranges from 1.5 mL to 5 mL and must be administered as a single intramuscular injection. Induration, redness and swelling at the injection site were observed in 13% of participants in the INVEGA HAFYERA group and 9% of participants in the INVEGA TRINZA group.[10] Investigator evaluation of injection site tenderness was higher for subjects in the INVEGA HAFYERA group versus the INVEGA TRINZA group (31% vs. 19%).[10] The most commonly observed adverse reactions observed with INVEGA HAFYERA administration included upper respiratory infection, injection site reaction, increased weight, headache and parkinsonism.[10]

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)
Clozapine	**CLOZARIL**	**4/2020**	**Warnings and Precautions**	CLOZARIL has potent anticholinergic effects. Treatment with CLOZARIL can result in central nervous system and peripheral anticholinergic toxicity, especially at higher dosages, or in overdose situations. Use with caution in patients with a current diagnosis or prior history of constipation, urinary retention, clinically significant prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions. When possible, avoid concomitant use with other anticholinergic medications because the risk for anticholinergic toxicity or severe gastrointestinal adverse reactions is increased.[11] Severe gastrointestinal adverse reactions have occurred with the use of CLOZARIL, primarily due to its potent anticholinergic effects and resulting gastrointestinal hypomotility. In post marketing experience, reported effects range from constipation to paralytic ileus. Increased frequency of constipation and delayed diagnosis and treatment increased the risk of severe complications of gastrointestinal hypomotility, resulting in intestinal obstruction, fecal impaction, megacolon and intestinal ischemia or infarction. These reactions have resulted in

				hospitalization, surgery, and death. The risk of severe adverse reactions is further increased with anticholinergic medications (and other medications that decrease gastrointestinal peristalsis); therefore, concomitant use should be avoided when possible.[11]
			Drug Interactions	Concomitant treatment with clozapine and other drugs with anticholinergic activity (e.g., benztropine, cyclobenzaprine, diphenhydramine) can increase the risk for anticholinergic toxicity and severe gastrointestinal adverse reactions related to hypomotility. Avoid concomitant use of CLOZARIL with anticholinergic drugs when possible.[11]
			Adverse Reactions	Restless leg syndrome, myocarditis, and polyserositis added to observed adverse effects in post marketing experiences.[11]

References:

1. Ceraso A, Lin JJ, Schneider-Thoma J, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev.* 2020(8).
2. Canadian Agency for Drugs and Technologies in Health (CADTH). Risperidone for Extended-Release Injectable Suspension (Perseris). https://www.cadth.ca/sites/default/files/DRR/2021/SR0671-Perseris-Combine.pdf November 2021. Accessed December 6, 2021.
3. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd ed. Washington (DC): American Psychiatric Association;2021: https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841 Accessed December 6, 2021.
4. Nasser AF, Henderson DC, Fava M, et al. Efficacy, Safety, and Tolerability of RBP-7000 Once-Monthly Risperidone for the Treatment of Acute Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study. *J Clin Psychopharmacol.* 2016;36(2):130-140.
5. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-276.
6. DelBello MP, Kadakia A, Heller V, et al. Systematic Review and Network Meta-analysis: Efficacy and Safety of Second-Generation Antipsychotics in Youths With Bipolar Depression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2021.
7. Finucane AM, Jones L, Leurent B, et al. Drug therapy for delirium in terminally ill adults. *Cochrane Database Syst Rev.* 2020;1(1):Cd004770.
8. Risperidone extended-release subcutaneous injection (PERSERIS) Prescribing Information. North Chesterfield, VA; Indivior, Inc. December 2019.
9. McDonagh MS DT, Selph S, et al. Treatments for Schizophrenia in Adults: A Systematic Review. Comparative Effectiveness Review No. 198. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10. Paliperidone palmitate extended-release injectable suspension (INVEGA HAFYERA) Prescribing Information. Titusville, NJ; Janssen Pharmaceuticals, Inc. August 2021.
11. Clozapine tablets (CLOZARIL) Prescribing Information. Rosemont, PA; HLS Therapeutics (USA), Inc. February 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER VIAL	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil,submicr.	ARISTADA INITIO	INTRAMUSC	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	INJECTION	AMPUL	Y
chlorpromazine HCl	THORAZINE	INJECTION	AMPUL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	INJECTION	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	INJECTION	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALDOL DECANOATE 50	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
risperidone	PERSERIS	SUBCUT	SUSER SYR	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
olanzapine	OLANZAPINE	INTRAMUSC	VIAL	V
olanzapine	ZYPREXA	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
paliperidone palmitate	INVEGA HAFYERA	INTRAMUSC	SYRINGE	V
ziprasidone mesylate	GEODON	INTRAMUSC	VIAL	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	INTRAMUSC	VIAL	V

Appendix 2: New Comparative Clinical Trials

A total of 5 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2021 & Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 29, 2021

1 exp CHLORPROMAZINE/	1826
2 exp HALOPERIDOL/	6299
3 exp FLUPHENAZINE/	326
4 exp ARIPIPRAZOLE/	2608
5 exp Paliperidone Palmitate/	923
6 exp RISPERIDONE/	6249
7 olanzapine	5865
8 ziprasidone.mp	1836
9 Schizophrenia/th [Therapy]	6471
10 Bipolar Disorder/th [Therapy]	3301
11 9 or 10	9396
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	21064
13 11 and 12	143
14 limit 13 to humans and english language	126
15 limit 14 to (clinical trial, phase iii or comparative study, or equivalence trial, or meta-analysis or multicenter study or practice guideline or randomized controlled trial)	33
16 limit 15 to years 2020-2021	5

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

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

Drug Class Literature Scan: Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS):

Focused update on angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and direct renin inhibitors (DRI)

Date of Review: February 2022

Date of Last Review: May 2017
Literature Search: 03/01/17 – 12/01/2021

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

Conclusions:

- There is moderate quality evidence of no significant effect on all-cause mortality, CV mortality or heart failure hospitalizations with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in patients with heart failure with preserved ejection fraction (HFpEF).[1,2]
- There is insufficient evidence to evaluate the benefits and harms of pharmacological interventions for heart failure in patients with chronic kidney disease.[3]
- There is low quality evidence that in patients with coronary artery disease (CAD) without heart failure, treatment with a renin-angiotensin-aldosterone system (RAAS) inhibitor may reduce the risk of all-cause mortality and CV mortality when compared to placebo but not when compared to active controls. Additionally, there is no benefit seen in trials with a lower baseline risk.[4]
- There is no evidence that ACEIs or ARBs increase the risk for COVID-19 infection, severe illness due to COVID-19 or death from COVID-19. Current guidance recommends against discontinuing ACEIs or ARBs due to this concern.
- There is no new comparative evidence that one ACEI or ARB is more effective or results in more harms than another agent.
- There is no new high-quality evidence evaluating the direct renin inhibitor (DRI) on clinical outcomes in patients with hypertension.

Recommendations:

- No further review or research is needed.
- No changes recommended based on clinical evidence.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

- There is moderate quality evidence of no difference between ACEIs and ARBs for total mortality, cardiovascular (CV) events, or CV mortality in patients with hypertension. Incidence of adverse effects was slightly lower for ARBs compared with ACEIs primarily due to a higher incidence of dry cough with ACEIs
- In patients with hypertension, moderate quality evidence demonstrates that compared with calcium channel blockers (CCBs), renin-angiotensin system

(RAS) inhibitors reduce death or hospitalizations for heart failure (HF) (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and end stage renal failure (ESRF) events

- Moderate quality evidence concluded the direct renin inhibitor (DRI), aliskiren, shows no benefit for the outcomes of major CV events, total mortality, cardiac death, myocardial infarction (MI), or stroke.
- There is moderate quality evidence that dual blockade of the RAS does not provide additional benefit in clinically relevant outcomes compared with monotherapy and increases risk of harm, specifically the risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events.
- Rename the "ACEIs, ARBs and DRIs" PDL class to "Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)" and include sacubitril/valsartan as a non-preferred agent in the class.
- Current prior authorization limits use of sacubitril/valsartan to patients with HFrEF with ejection fraction < 40%, on maximally tolerated ACE-I or ARB and a recommended beta-blocker.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) comparing angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and direct renin inhibitors (DRI) on clinically relevant outcomes to active controls, or placebo if needed, was conducted. Sacubitril/valsartan and vericiguat were excluded from the review since they were recently evaluated. 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:

After review, 11 systematic reviews were excluded due to poor quality[5-8], wrong study design of included trials (e.g., observational)[9-12], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[13-15].

<u>Heart Failure</u>

A systematic review and meta-analysis evaluated the effects of treatments on mortality, hospitalizations, functional status and biomarker levels in patients with heart failure with preserved ejection fraction (HFpEF), defined as left ventricular ejection fraction (LVEF) ≥ 40%.[2] Randomized controlled trials (RCTs) comparing drug therapy with placebo, no treatment or standard medical treatment with a minimum follow-up of 12 weeks and evaluating cardiovascular (CV) outcomes were included. Trials were assessed for bias using the Cochrane Collaboration risk of bias tool and Egger test was done for publication bias. Overall, 27 articles were included in the analysis. Five were found to have high risk of bias and the remainder with low risk. Pooled analysis of ACEI's (RR 1.10; 95% CI 0.86 to 1.43) and ARBs (RR 1.02; 95% CI 0.93 to 1.12) showed no significant effect on all-cause mortality compared with control. [2] There was also no significant effect on CV mortality with ACEIs (RR 0.94; 5% CI 0.62 to 1.43) or ARBs (RR 1.02; 95% CI 0.90 to 1.14) compared to controls. [2] Pooled effects of all drugs blocking the renin-angiotensin-

aldosterone system (RAAS) showed a reduced risk for heart failure hospitalization (RR 0.90; 95% CI 0.82 to 0.98; p=0.01), with no effect seen with ACEIs or ARBs individually. [2] There were no meaningful effects when stratified by mean LVEF.

The Cochrane Collaboration evaluated the benefits and harms of pharmacological interventions for heart failure (HF) in people with HF and chronic kidney disease (CKD).[3] Randomized controlled trials of any pharmacological intervention for acute or chronic HF (with both preserved and reduced EF) and CKD were included. The primary outcomes were death and HF hospitalizations. There were 112 studies that met inclusion criteria for qualitative review with a significant number with unclear risk of bias, including selection, detection and other bias. Only 26 studies included extractable data that was included in the meta-analysis. Generally, there was insufficient evidence to make strong conclusions about the clinical effects of pharmacological interventions for HF in persons with CKD and further studies are needed to better define the clinical benefit derived with pharmacological interventions.[3] There was low quality evidence demonstrating no significant effect on all cause morality (RR 0.85; 95% CI 0.70 to 1.02; 4 studies) or CV mortality (RR 0.81; 95% CI 0.64 to 1.01; 2 studies) with ACE-Is or ARBs versus placebo and very low-quality evidence of no significant effect on HF hospitalization (RR 0.90; 95% CI 0.43 to 1.90; 2 studies).[3] There was no data on quality of life, worsening heart failure, all-cause hospitalization or worsening kidney function.

The Cochrane Collaboration assessed the effects of beta-blockers and inhibitors of the RAAS for chronic HFpEF, defined by LVEF ≥ 40%.[1] A total of 41 RCTs (n=23,492) were included. The risk of bias was often unclear with only five studies having a low risk of bias in all domains. Eight studies were identified evaluating ACEIs (n=2061). There was moderate quality evidence that ACEI likely has little or no effect on CV mortality (RR 0.93; 95% CI 0.61 to 1.42; 2 studies), all-cause mortality (RR 1.04; 95% CI 0.75 to 1.45; 5 studies) and heart failure hospitalizations (RR 0.86; 95% CI 0.64 to 1.15; 3 studies) and low-quality evidence of little or no effect on quality of life (mean difference [MD] -0.09; 95% CI -3.66 to 3.48; 2 studies). [1] There were limited data on hyperkalemia and no large clinical trials with more than 1000 participants. Pooled analysis of 8 studies (n=8755) with ARBs found high quality evidence of little or no effect on CV mortality (RR 1.02; 95% 0.90 to 1.14; 3 studies), all-cause mortality (RR 1.01; 95% CI 0.92 to 1.11; 4 studies), HF hospitalizations (RR 0.92; 95% CI 0.83 to 1.02; 3 studies), and quality of life (MD 0.41; 95% CI -0.86 to 1.67; 3 studies). [1] ARBs were associated with a higher risk of hyperkalemia (RR 1.88; 95% CI 1.07 to 3.33; 2 studies). [1] Unlike ACEIs and ARBs, there was moderate quality evidence of modest reduction in heart failure hospitalizations with angiotensin receptor neprilysin inhibitors (ARNIs) and mineralocorticoid receptor antagonists (MRAs), but no effect on all-cause or CV mortality. [1]

Hypertension

An update to the systematic review and meta-analysis evaluating pharmacotherapy for hypertension (HTN) in adults 60 years or older was recently released from the Cochrane collaboration.[16] The objective of the analysis was to quantify the benefit of antihypertensive medications compared to placebo or no treatment on all-cause mortality in people 60 years and older with mild to moderate HTN (blood pressure ≥ 140/90 mmHg). RCTs of at least one year duration were included. A total of 16 trials were included (n=26,795) in ambulatory patients with an average blood pressure of 182/95 mmHg. [16] Most trials evaluated thiazide type diuretics with a mean treatment duration of 3.8 years. At least one trial included an ACEI based treatment arm and many included subjects on background ACEI therapy. When treatments were pooled, there was a reduction in all-cause mortality with treatment versus control (10% vs. 11%; relative risk [RR] 0.91; 95% CI 0.85 to 0.97, moderate quality evidence of a reduction in CV mortality (9.8% vs. 13.6%; RR 0.72; 95% CI 0.68 to 0.77). [16] There was also moderate quality evidence of a reduction in cerebrovascular mortality and morbidity (RR 0.66; 95% CI 0.59 to 0.74) and coronary heart disease mortality and morbidity (RR 0.78; 95% CI 0.69 to 0.88). [16] Withdrawals due to adverse effects were increased with treatment (15.7%) versus control (5.4%) (RR 2.91; 95% CI 2.65 to 3.30). [16] Since the previous systematic review, only one additional trial was identified and added. Subgroup analysis demonstrates a higher magnitude of benefit in the 60- to 79-year-old patients compared to those over the age of 80. [16] This review did not evaluate differences based on the medication that was studied.

Coronary Artery Disease

Inhibitors of RAAS (ACEIs or ARBs) were evaluated in patients with coronary artery disease (CAD) without heart failure in a systematic review and meta-analysis of RCTs with at least one year of follw-up.[4] Trials were assessed for risk of bias using the Cochrane Collaboration tool. Primary outcomes were all-cause mortality, CV death, MI, stroke, angina, and heart failure. Literature search identified 24 trials (n=61,961) with an average follow up for 3.2 years. [4] Eighteen trials were placebo controlled and seven included an active control, including calcium channel blockers, thiazide diuretics and conventional treatment. RAAS inhibitors significantly reduced the risk of all-cause mortality compared to placebo (RR 0.84; 95% CI 0.72 to 0.98) but not when compared to active controls (RR 1.05; 95% CI 0.94 to 1.17).[4] Treatment with a RAAS inhibitor also reduced the risk of CV mortality (RR 0.74; 95% CI 0.59 to 0.94) and MI (RR 0.82; 95% CI 0.76 to 0.88) when compared to placebo but not when compared with active controls (RR 1.08; 95% CI 0.93 to 1.25 for CV mortality and RR 0.99; 95% CI 0.87 to 1.12 for MI). [4] Meta-regression analysis showed that the effect of RAAS inhibition on all-cause mortality, CV mortality and MI depended on control event rate with more benefit in trials with a high baseline risk but no benefit seen in trials with a lower baseline risk. Similarly, RAAS inhibitors reduced the risk of stroke, angina and heart failure when compared to placebo in patients with CAD without heart failure. [4]

New Guidelines:

Four guidelines were excluded due to poor quality rigor of development and systematic approach.[17-20] Two of these are consensus statements.[17,18]

Heart Failure:

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Focused Update of the 2013 Guideline on the Management of Heart Failure[21]

The 2017 focused update of the 2013 guideline included revisions on biomarkers, new therapies for HFrEF, updates on HFpEF and new data on important comorbidities. Part 1 of this guideline included an update on new pharmacological therapy, including sacubitril/valsartan in HFrEF, and was reviewed in a previous class update. There were no major changes to recommendations regarding therapy with an RAAS inhibitors in this update. There remains a Class I recommendation based on level A evidence that in patients with chronic symptomatic HFrEF an ACEI or ARB should be initiated in combination with evidence-based beta blockers to reduce morbidity and mortality. There is also a Class I recommendation with level B-R evidence to consider angiotensin receptor-neprilysin inhibitor (ARNI). An ARNI should not be administered concomitantly with ACE-I or within 36 hours of the last dose due to the risk of angioedema. The update included a new Class I recommendation (level of evidence B-R) to replace ACEI or ARB with ARNI in those who tolerate therapy.

National Institute for Health and Care Excellence (NICE): Chronic heart failure in adults: diagnosis and management.[22]

The NICE updated its guidelines for chronic heart failure in adults in 2018. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The guidelines recommend first-line therapy with an ACE-I and beta blocker for those patients with HFrEF. An ARB is recommended as an alternative to ACEI for those with intolerable side effects with ACEI. The following are key guideline statements regarding therapy with sacubitril/valsartan:

- Sacubitril/valsartan is recommended as an option for treatment symptomatic chronic HFrEF, only in people:
  - With NYHA class II to IV symptoms, and
  - Left ventricular ejection fraction of 35% or less, and
  - Who are already taking a stable dose of an ACEI or ARB
- Treatment with sacubitril/valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team

Hypertension:

Department of Veterans Affairs (VA)/Department of Defense (DoD): Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care setting[23]

The VA/DoD HTN guidelines were updated in 2020 based on a systematic review of the literature and using the GRADE framework to evaluate the body of evidence and strength of recommendations. It is intended to assist healthcare providers in the screening, diagnosis and management of HTN.[23] These guidelines include a weak recommendation to treat to a systolic BP of < 130 mmHg with a strong recommendation for < 150 mmHg for patients 60 years and over and < 140 mmHg for those 60 years and over with type 2 diabetes.[23] When drug therapy is initiated in the general population, it is strongly recommended to use one or more of the following as first line treatment: 1) Thiazide-type diuretics, 2) ACEIs or ARBs, or 3) long-acting calcium channel blockers (CCBs).[23] This recommendation was based on reviews of systematic review and meta-analysis of 50 RCTs that found no difference between ACEIs and ARBs, ACEs and thiazide-type diuretics, and ACEIs and CCBs. There are no specific recommendations made for individual medications within each class. For patients unlikely to achieve goal with monotherapy, it is recommended to consider initiating treatment with combination therapy.[23] There is also a strong recommendation against using ACEIs, ARBs, or DRIs in combination due to the increased risk for harm (kidney dysfunction and hyperkalemia). Additional recommendations are made for the following specific populations:

Population	*Recommendation*	*Strength*
• Patients aged 65 years and older	Thiazide-type diuretic as first line	Weak for
• African American patients	Avoid ACEI or ARB as monotherapy	Strong against
• Patients with CKD and albuminuria	ACEI or ARB to slow progression of CKD	Strong for
• Resistant HTN	Adding spironolactone	Weak for

National Institute for Health and Care Excellence (NICE): Hypertension in adults: diagnosis and management.[24]

The NICE updated its guidelines for chronic hypertension in adults in 2019. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The following recommendations are included for RAAS inhibitors:

- The updated guidelines recommend starting an ACEI or ARB in adults with:
  - Type 2 diabetes
  - Under 55 years old but not of black African or African-Caribbean family origin
- If an ACEI is not tolerated, offer an ARB to treat HTN
- Do not combine an ACEI or ARB to treat HTN
- If HTN is not controlled with a CCB, offer an ACEI, ARB or thiazide-like diuretic in combination
- If HTN is not controlled in adults of black African or African-Caribbean family origin who do not have type 2 diabetes, consider an ARB, in preference to an ACEI, in addition to initial step 1 treatment

COVID-19:
Since SARS-CoV-2 enters cells by binding the viral spike protein to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2), there was initial concern that ACEI and ARBs could be harmful in patients with Covid-19 due to upregulation of ACE2 expression and increasing the availability of targets for SARS-CoV2.[25] Although mostly observational, current data does not provide evidence to support the theory that ACEIs or ARBs are associated with increased risks for those with COVID-19. Two randomized, open-label prospective trials (n=356) in patients hospitalized with COVID-19 have confirmed that discontinuation of ACEI or ARB did not impact severity or mortality associated with COVID-19 over 30 days.[26,27] These trials enrolled participants between March and August of 2020, prior to emergence of COVID variants, including the Delta variant.

Multiple professional scientific societies and COVID-19 guideline panels have recommended that patients should not discontinue ACEI or ARB therapy due to concern for increased risk for infection, severe illness, or death during the COVID-19 pandemic. This includes the American Heart Association/Heart Failure Society of America/American College of Cardiology[28], European Society of Cardiology[29], Canadian Cardiovascular Society[30], and the National Institutes of Health (NIH) COVID-19 Treatment Guidelines.[31]

New Formulations:
Two new formulations were approved since the last update. A new oral solution of valsartan (Prexxartan®) was FDA approved in 11/2017 and a new formulation of aliskiren (Tekturna®) oral pellets was also approved in 11/2017. However, both formulations have since been since been removed from the market.

New FDA Safety Alerts:
Contraindications, Warnings and Precautions and Drug Interactions were updated for all ACEI to include the increased risk of angioedema when an ACEI is administered within 36 hours of a neprilysin inhibitor, including sacubitril/valsartan. For patients taking an ACEI, it must be stopped and allow for a 36-hour washout period prior to starting sacubitril/valsartan.[21]

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)
ACE Inhibitors Sacubitril/valsartan	NA Entresto®	07/2017	Contraindications, Warnings, Drug Interactions	Create alerts to warn against the concomitant use of Entresto and ACE inhibitors when claims are submitted for both drugs.

References:

1. Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev*. May 22 2021;5(5):Cd012721. doi:10.1002/14651858.CD012721.pub3
2. Zheng SL, Chan FT, Nabeebaccus AA, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart (British Cardiac Society)*. Mar 2018;104(5):407-415. doi:10.1136/heartjnl-2017-311652
3. Lunney M, Ruospo M, Natale P, et al. Pharmacological interventions for heart failure in people with chronic kidney disease. *Cochrane Database Syst Rev*. Feb 27 2020;2(2):Cd012466. doi:10.1002/14651858.CD012466.pub2
4. Bangalore S, Fakheri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. *BMJ (Clinical research ed)*. Jan 19 2017;356:j4. doi:10.1136/bmj.j4
5. Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-Analysis Evaluating the Effects of Renin-Angiotensin-Aldosterone System Blockade on Outcomes of Heart Failure With Preserved Ejection Fraction. *The American journal of cardiology*. Apr 15 2020;125(8):1187-1193. doi:10.1016/j.amjcard.2020.01.009
6. Xie W, Zheng F, Evangelou E, et al. Blood pressure-lowering drugs and secondary prevention of cardiovascular disease: systematic review and meta-analysis. *J Hypertens*. Jun 2018;36(6):1256-1265. doi:10.1097/hjh.0000000000001720
7. Coleman CI, Weeda ER, Kharat A, Bookhart B, Baker WL. Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on renal and mortality outcomes in people with Type 2 diabetes and proteinuria. *Diabet Med*. Jan 2020;37(1):44-52. doi:10.1111/dme.14107
8. Dimou C, Antza C, Akrivos E, et al. A systematic review and network meta-analysis of the comparative efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in hypertension. *J Hum Hypertens*. Mar 2019;33(3):188-201. doi:10.1038/s41371-018-0138-y
9. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. *Pharmacol Res*. Aug 2020;158:104927. doi:10.1016/j.phrs.2020.104927
10. Mackey K, Kansagara D, Vela K. Update Alert 7: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults. *Annals of internal medicine*. Feb 2021;174(2):W25-w29. doi:10.7326/l20-1446
11. Flacco ME, Acuti Martellucci C, Bravi F, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. *Heart (British Cardiac Society)*. Oct 2020;106(19):1519-1524. doi:10.1136/heartjnl-2020-317336
12. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. *Annals of internal medicine*. Aug 4 2020;173(3):195-203. doi:10.7326/m20-1515
13. Haynes R, Judge PK, Staplin N, et al. Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease. *Circulation*. Oct 9 2018;138(15):1505-1514. doi:10.1161/circulationaha.118.034818
14. Hansen MR, Hróbjartsson A, Videbæk L, et al. Postponement of Death by Pharmacological Heart Failure Treatment: A Meta-Analysis of Randomized Clinical Trials. *The American journal of medicine*. Jun 2020;133(6):e280-e289. doi:10.1016/j.amjmed.2019.11.015
15. Bjerre HL, Christensen JB, Buus NH, Simonsen U, Su J. The role of aliskiren in the management of hypertension and major cardiovascular outcomes: a systematic review and meta-analysis. *J Hum Hypertens*. Nov 2019;33(11):795-806. doi:10.1038/s41371-018-0149-8
16. Musini VM, Tejani AM, Bassett K, Puil L, Wright JM. Pharmacotherapy for hypertension in adults 60 years or older. *Cochrane Database Syst Rev*. Jun 5 2019;6(6):Cd000028. doi:10.1002/14651858.CD000028.pub3

17. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. Oct 15 2019;74(15):1966-2011. doi:10.1016/j.jacc.2019.08.001
18. Maddox TM, Januzzi JL, Jr., Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. Feb 16 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022
19. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Can J Cardiol*. Apr 2021;37(4):531-546. doi:10.1016/j.cjca.2021.01.017
20. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens*. Jun 2020;38(6):982-1004. doi:10.1097/hjh.0000000000002453
21. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. Aug 8 2017;136(6):e137-e161. doi:10.1161/cir.0000000000000509
22. National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management (NICE guideline NG106) 2018. https://www.nice.org.uk/guidance/ng106.
23. VA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. 2020. Available at: https://www.healthquality.va.gov/guidelines/cd/htn/index.asp Accessed: November 15, 2021.
24. National Institute for Health and Care Excellence. Chronic hypertension in adults: diagnosis and management (NICE guideline NG136) 2019. Available at: https://www.nice.org.uk/guidance/ng136.
25. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *The New England journal of medicine*. Jun 18 2020;382(25):2441-2448. doi:10.1056/NEJMoa2008975
26. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *The Lancet Respiratory medicine*. Mar 2021;9(3):275-284. doi:10.1016/s2213-2600(20)30558-0
27. Lopes RD, Macedo AVS, de Barros ESPGM, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. *Jama*. Jan 19 2021;325(3):254-264. doi:10.1001/jama.2020.25864
28. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. *J Card Fail*. May 2020;26(5):370. doi:10.1016/j.cardfail.2020.04.013
29. European Society of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. March 13, 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang (Accessed November 28 2021).
30. Canadian Cardiovascular Society. Guidance from the CCS COVID-19 Rapid Response team. March 20, 2020. https://www.ccs.ca/images/Images_2020/CCS_CHFS_Update_COVID__CV_medications_Mar20.pdf. (Accessed November 28 2021).
31. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 11/28/21.

32. Marciniak TA, Serebruany V. Ranolazine, ACE Inhibitors, and Angiotensin Receptor Blockers. *The American journal of medicine*. Dec 2019;132(12):e844-e845. doi:10.1016/j.amjmed.2019.02.032
33. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart (British Cardiac Society)*. Oct 2020;106(19):1503-1511. doi:10.1136/heartjnl-2020-317393
34. Park S, Kim YG, Ann SH, et al. Angiotensin-Converting Enzyme Inhibitor-based Versus Angiotensin Receptor Blocker-based Optimal Medical Therapy After Percutaneous Coronary Intervention: A Nationwide Cohort Study. *J Cardiovasc Pharmacol*. Jan 1 2021;77(1):61-68. doi:10.1097/fjc.0000000000000930
35. Mullen M, Jin XY, Child A, et al. Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet (London, England)*. Dec 21 2019;394(10216):2263-2270. doi:10.1016/s0140-6736(19)32518-8
36. Mehlum MH, Liestøl K, Kjeldsen SE, et al. Blood Pressure-Lowering Profiles and Clinical Effects of Angiotensin Receptor Blockers Versus Calcium Channel Blockers. *Hypertension (Dallas, Tex : 1979)*. Jun 2020;75(6):1584-1592. doi:10.1161/hypertensionaha.119.14443

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
enalapril maleate	VASOTEC	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
olmesartan medoxomil	BENICAR	ORAL	TABLET	Y
olmesartan medoxomil	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
ramipril	ALTACE	ORAL	CAPSULE	Y
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
aliskiren hemifumarate	ALISKIREN	ORAL	TABLET	N
aliskiren hemifumarate	TEKTURNA	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
candesartan cilexetil	ATACAND	ORAL	TABLET	N
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
enalapril maleate	ENALAPRIL MALEATE	ORAL	SOLUTION	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N
perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N
quinapril HCl	ACCUPRIL	ORAL	TABLET	N
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	N
sacubitril/valsartan*	ENTRESTO	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
Vericiguat*	VERQUVO	ORAL	TABLET	

* These products were reviewed in June 2021 and are not the focus of this literature scan.

Appendix 2: New Comparative Clinical Trials

A total of 19 citations were manually reviewed from the initial literature search and after initial review of title and abstract (excluding trials with sacubitril/valsartan), 6 were included for more detailed evaluation. Two of these were systematic reviews and are included above. After further review, 3 citations were excluded because of wrong study design (eg, observational)[32-34], population[35], comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results		Notes/Limitations
Mehlum et al.[36] MC, DB, RCT	Valsartan (V) 80 mg versus amlodipine (A) 5 mg *doses were titrated up to goal BP of < 140/90 mm Hg	Patients with HTN and ≥1 additional CV risk factor N=14,996	Non-fatal or fatal MI, stroke, CHF, and death	<u>MI</u> V: 363 (4.8%) A: 306 (4.1%) HR 1.19; 95% CI 1.02-1.39; p=0.03 <u>Stroke:</u> V: 312 (4.1%) A: 277 (3.7%) HR 1.13; 95% CI 0.96-1.33; p=0.1	<u>CHF:</u> V:292 (3.9%) A: 340 (4.5%) HR 0.86; 95% CI 0.74-1.00; p=0.06 <u>Death:</u> V: 802 (10.7%) A: 792 (10.6%) HR 1.01; 95% CI 0.92-1.12; p=0.8	Posthoc analysis of VALUE trial

Abbreviations: BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; DB = double blind; HR = hazard ratio; HTN = hypertension; MC = multicenter; MI = myocardial infarction; RCT = randomized clinical trial

Mehlum M, Liestol K, Kjeldsen S, et al. Blood Pressure-Lowering Profiles and Clinical Effects of Angiotensin Receptor Blockers Versus Calcium Channel Blockers *Hypertension*. 2020 Jun;75(6):1584-1592. doi: 10.1161/HYPERTENSIONAHA.119.14443. Epub 2020 Apr 27.

Abstract

Blood pressure-lowering drugs have different blood pressure-lowering profiles. We studied if differences in blood pressure mean and variability can explain the differences in risks of cardiovascular events and death among 15 245 high-risk hypertensive patients randomized to valsartan or amlodipine and followed for 4.2 years in the VALUE trial (Valsartan Antihypertensive Long-Term Use Evaluation). We selected patients with ≥3 visits and performed Cox regression analyses, defining mean blood pressure as a time-dependent covariate and visit-to-visit and within-visit blood pressure variability as the SD. Of 14 996 eligible patients, participants in the valsartan group had higher systolic mean blood pressure by 2.2 mm Hg, higher visit-to-visit systolic variability by 1.4 mm Hg, and higher within-visit systolic variability by 0.2 mm Hg (P values <0.0001). The higher risks of myocardial infarction and stroke in the valsartan group was attenuated after adjustment for mean and variability of systolic blood pressure, from HR 1.19 (95% CI, 1.02-1.39) to 1.11 (0.96-1.30) and from HR 1.13 (0.96-1.33) to 1.00 (0.85-1.18), respectively. The lower risk of congestive heart failure in the valsartan group was accentuated after adjustment, from HR 0.86 (0.74-1.00) to 0.76 (0.65-0.89). A smaller effect was seen on risk of death, from 1.01 (0.92-1.12) to 0.94 (0.85-1.04). In conclusion, the higher risks of myocardial infarction and stroke in patients randomized to valsartan versus amlodipine were related to the drugs' different blood pressure modulating profiles. The risk of congestive heart failure with valsartan was lower, independent of the less favorable blood pressure modulating profile.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to December 1, 2021>

1	losartan.mp. or Losartan/	10248
2	olmesartan.mp.	1718
3	telmisartan.mp.	2601
4	candesartan.mp.	3401
5	eprosartan.mp.	414
6	irbesartan.mp.	1982
7	valsartan.mp.	4837
8	azilsartan.mp.	252
9	angiotensin receptor blocker.mp. or Angiotensin Receptor Antagonists/	12158
10	benazepril.mp.	836
11	angiotensin converting enzyme inhibitors.mp. or Angiotensin-Converting Enzyme Inhibitors/	40823
12	enalapril.mp. or Enalapril/	8326
13	lisinopril.mp. or Lisinopril/	3104
14	ramipril.mp. or Ramipril/	2922
15	captopril.mp. or Captopril/	13587
16	fosinopril.mp. or Fosinopril/	626
17	moexipril.mp.	116
18	perindopril.mp. or Perindopril/	2321
19	quinapril.mp. or Quinapril/	838
20	aliskiren.mp.	1280
21	direct renin inhibitors.mp.	179
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	76982
23	Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular outcomes.mp. or Coronary Artery Disease/	394667
24	cardiovascular mortality.mp.	15148
25	23 or 24	402320
26	22 and 25	8080
27	limit 26 to (english language and full text and humans and yr="2017 -Current" and (clinical trial, all or comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or "systematic review"))	81
28	from 27 keep 1,6,14,18,22,24,30-31,35-36,42,45,54,56,62,66,72-73,78	19
29	from 28 keep 4,6,8,10,14,18	6

Appendix 5: Key Inclusion Criteria

Population	**Cardiovascular disease or high cardiovascular risk**
Intervention	ACE-I, ARB, DRI
Comparator	Active control or placebo
Outcomes	Major adverse cardiovascular events, cardiovascular mortality, all-cause mortality, renal outcomes
Timing	≥ 3 months
Setting	Outpatient setting for follow up

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

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
ropeginterferon alfa-2b-njft	BESREMI
sirolimus albumin-bound nanoparticles	FYARRO

Recommendation:

- Update prior authorization criteria to include new, recently approved antineoplastic drugs.

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.

Approval Criteria		
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
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.

Approval Criteria
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 1/4/2022)
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
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG

Generic Name	Brand Name
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
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
dostarlimab-gxly	JEMPERLI
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

Generic Name	Brand Name
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mobecertinib	EXKIVITY
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA

Generic Name	Brand Name
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
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
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO

Generic Name	Brand Name
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
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
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

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2020 - June 2021

Eligibility	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Total Members (FFS & Encounter)	1,065,127	1,078,611	1,091,643	1,105,304	1,124,250	1,142,287	1,155,608	1,165,327	1,176,534	1,186,439	1,195,359	1,203,243	1,140,811
FFS Members	92,036	97,318	96,060	99,759	110,699	110,136	110,971	104,212	106,887	108,646	109,364	105,833	104,327
OHP Basic with Medicare	7,235	7,333	7,140	7,395	8,031	7,925	7,781	7,599	7,743	7,998	8,048	7,967	7,683
OHP Basic without Medicare	11,469	11,624	11,493	11,546	11,692	11,422	11,524	11,224	11,074	11,063	11,039	10,911	11,340
ACA	73,332	78,361	77,427	80,818	90,976	90,789	91,666	85,389	88,070	89,585	90,277	86,955	85,304
Encounter Members	973,091	981,293	995,583	1,005,545	1,013,551	1,032,151	1,044,637	1,061,115	1,069,647	1,077,793	1,085,995	1,097,410	1,036,484
OHP Basic with Medicare	72,537	72,713	73,520	74,103	74,533	75,527	76,328	77,441	78,598	79,521	80,356	81,391	76,381
OHP Basic without Medicare	62,587	64,059	65,009	65,428	65,582	66,083	67,172	67,155	66,975	67,232	67,380	67,600	66,022
ACA	837,967	844,521	857,054	866,014	873,436	890,541	901,137	916,519	924,074	931,040	938,259	948,419	894,082

Gross Cost Figures for Drugs	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	YTD Sum
Total Amount Paid (FFS & Encounter)	$90,469,597	$88,014,125	$88,718,452	$89,878,823	$86,356,029	$97,867,589	$93,379,926	$89,633,288	$105,345,405	$100,544,795	$97,755,894	$104,295,429	$1,132,259,354
Mental Health Carve-Out Drugs	$9,468,980	$9,174,782	$9,229,001	$9,450,992	$9,149,232	$10,068,420	$10,189,810	$10,200,587	$12,117,144	$11,754,249	$11,391,924	$12,053,790	$124,248,913
OHP Basic with Medicare	$32,866	$30,054	$38,156	$25,916	$26,636	$43,711	$26,605	$27,401	$8,529	$7,638	$5,904	$5,729	$279,143
OHP Basic without Medicare	$3,564,559	$3,591,312	$3,566,715	$3,691,659	$3,621,907	$3,904,114	$4,009,341	$4,076,052	$4,680,967	$4,598,122	$4,351,713	$4,650,257	$48,306,718
ACA	$5,829,824	$5,503,762	$5,577,427	$5,686,192	$5,445,824	$6,066,550	$6,100,090	$6,038,667	$7,358,878	$7,067,994	$6,954,332	$7,312,154	$74,941,696
FFS Physical Health Drugs	$2,559,091	$2,371,978	$2,482,914	$2,574,584	$2,299,723	$2,595,390	$4,476,668	$4,156,472	$5,049,483	$4,750,153	$4,377,648	$4,823,548	$42,517,652
OHP Basic with Medicare	$56,118	$48,367	$48,223	$47,671	$43,752	$48,463	$160,407	$142,234	$157,460	$161,468	$165,026	$175,065	$1,254,254
OHP Basic without Medicare	$870,473	$848,072	$867,036	$922,623	$775,671	$942,688	$1,356,464	$1,131,667	$1,270,848	$1,224,263	$1,014,925	$1,181,939	$12,406,670
ACA	$1,484,344	$1,348,971	$1,437,998	$1,491,424	$1,366,652	$1,474,213	$2,840,651	$2,764,979	$3,501,164	$3,209,483	$3,080,207	$3,326,341	$27,326,425
FFS Physician Administered Drugs	$1,574,901	$1,143,789	$1,099,112	$1,628,518	$1,265,639	$1,221,043	$1,501,282	$1,810,876	$1,594,270	$1,336,435	$1,150,783	$1,683,832	$17,010,481
OHP Basic with Medicare	$130,913	$88,598	$100,427	$83,981	$106,382	$100,059	$172,681	$166,760	$145,299	$105,025	$150,867	$116,562	$1,467,554
OHP Basic without Medicare	$495,740	$239,681	$241,384	$607,085	$392,520	$250,041	$332,075	$783,219	$455,384	$282,236	$266,429	$739,640	$5,085,433
ACA	$391,611	$373,543	$390,662	$462,017	$354,628	$473,659	$515,595	$481,541	$472,914	$508,613	$359,505	$385,838	$5,170,125
Encounter Physical Health Drugs	$60,902,059	$59,347,805	$60,157,406	$59,976,344	$58,136,419	$63,073,514	$60,783,504	$58,130,839	$68,451,101	$65,055,616	$63,519,872	$67,145,868	$744,680,346
OHP Basic with Medicare	$677,710	$652,717	$742,679	$758,718	$718,169	$761,320	$622,884	$587,803	$381,279	$424,888	$392,162	$456,508	$7,176,837
OHP Basic without Medicare	$14,032,986	$14,323,346	$14,659,777	$14,226,252	$14,407,286	$15,841,008	$14,931,161	$14,190,949	$16,783,879	$16,005,180	$15,509,099	$16,380,953	$181,291,877
ACA	$45,562,789	$43,746,165	$44,122,184	$44,254,217	$42,326,321	$45,800,408	$44,567,219	$42,663,311	$50,405,715	$47,777,265	$46,812,575	$49,269,555	$547,307,723
Encounter Physician Administered Drugs	$15,964,565	$15,975,771	$15,750,020	$16,248,385	$15,505,017	$20,909,222	$16,428,661	$15,334,515	$18,133,407	$17,648,342	$17,315,666	$18,588,391	$203,801,961
OHP Basic with Medicare	$641,851	$606,307	$658,424	$649,763	$635,391	$628,865	$764,430	$662,332	$989,816	$897,357	$889,958	$909,344	$8,933,839
OHP Basic without Medicare	$3,285,941	$3,428,006	$3,629,263	$3,725,768	$3,471,211	$7,202,371	$3,733,395	$3,145,622	$3,799,852	$3,683,572	$4,101,823	$3,983,799	$47,190,623
ACA	$11,662,871	$11,543,106	$10,995,447	$11,436,031	$10,869,836	$12,743,053	$11,491,629	$11,070,614	$12,995,612	$12,724,817	$12,032,541	$13,509,728	$143,075,284

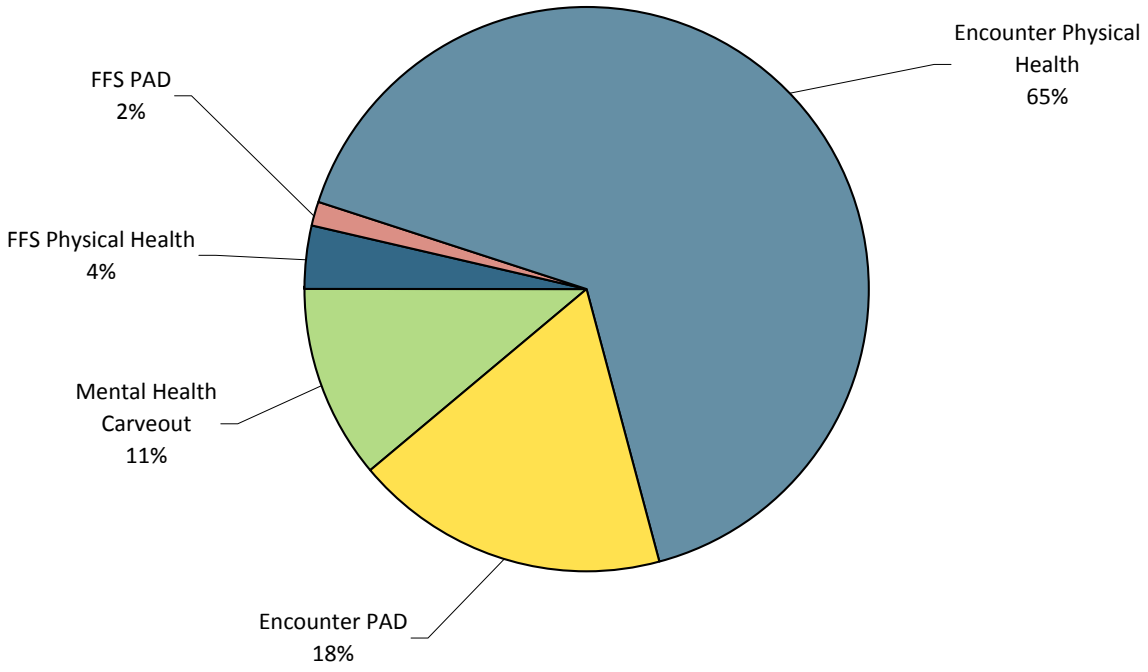
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

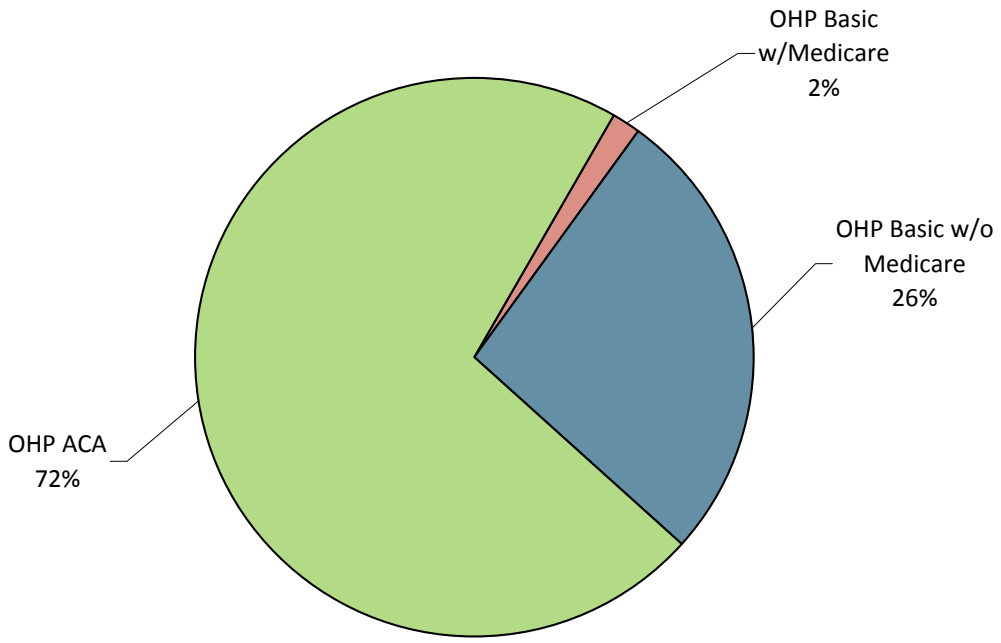
Last Updated: January 20, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2020 - June 2021

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

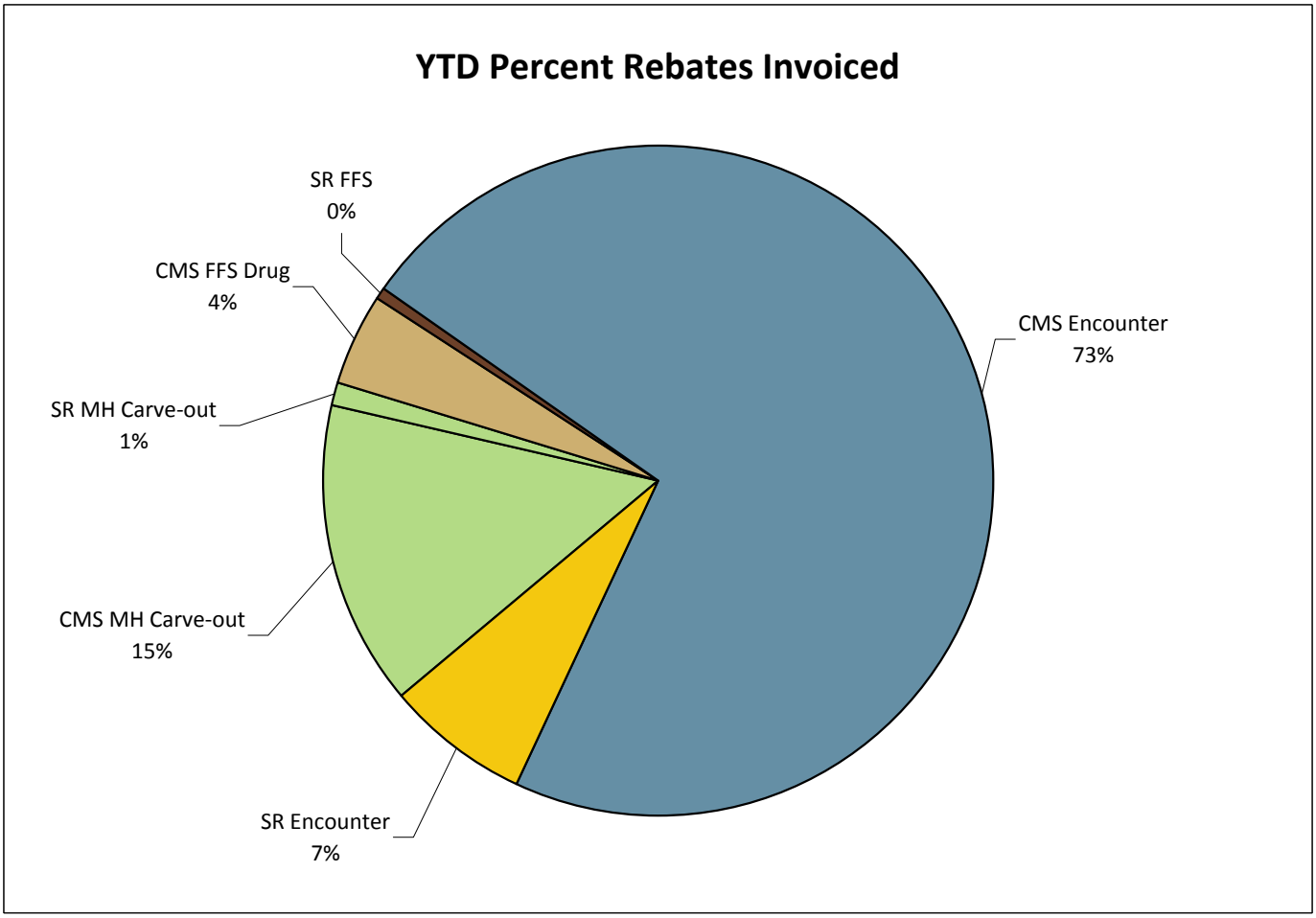
Last Updated: January 20, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2020 - June 2021

Quarterly Rebates Invoiced	2020-Q3	2020-Q4	2021-Q1	2021-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$115,623,234	$109,072,362	$117,492,895	$122,464,082	$464,652,573
CMS MH Carve-out	$18,683,792	$13,100,168	$16,652,526	$19,356,010	$67,792,495
SR MH Carve-out	$1,335,658	$1,460,762	$1,484,788	$1,417,742	$5,698,950
CMS FFS Drug	$4,683,334	$4,667,015	$6,049,688	$5,336,811	$20,736,848
SR FFS	$458,027	$512,651	$540,732	$512,939	$2,024,348
CMS Encounter	$83,133,845	$81,645,841	$84,329,354	$87,010,869	$336,119,909
SR Encounter	$7,328,579	$7,685,925	$8,435,807	$8,829,712	$32,280,022

Quaterly Net Drug Costs	2020-Q3	2020-Q4	2021-Q1	2021-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$151,578,940	$165,030,079	$170,865,725	$180,132,036	$667,606,781
Mental Health Carve-Out Drugs	$7,853,314	$14,107,715	$14,370,227	$14,426,212	$50,757,468
FFS Phys Health + PAD	$6,090,424	$6,405,231	$11,998,631	$12,272,651	$36,766,936
Encounter Phys Health + PAD	$137,635,203	$144,517,133	$144,496,866	$153,433,174	$580,082,376



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

Last Updated: January 20, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: July 2020 - June 2021

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$84.94	$81.60	$81.27	$81.32	$76.81	$85.68	$80.81	$76.92	$89.54	$84.75	$81.78	$86.68	$82.67
Mental Health Carve-Out Drugs	$8.89	$8.51	$8.45	$8.55	$8.14	$8.81	$8.82	$8.75	$10.30	$9.91	$9.53	$10.02	$9.06
FFS Physical Health Drugs	$27.81	$24.37	$25.85	$25.81	$20.77	$23.57	$40.34	$39.88	$47.24	$43.72	$40.03	$45.58	$33.75
FFS Physician Administered Drugs	$17.11	$11.75	$11.44	$16.32	$11.43	$11.09	$13.53	$17.38	$14.92	$12.30	$10.52	$15.91	$13.64
Encounter Physical Health Drugs	$62.59	$60.48	$60.42	$59.65	$57.36	$61.11	$58.19	$54.78	$63.99	$60.36	$58.49	$61.19	$59.88
Encounter Physician Administered Drugs	$16.41	$16.28	$15.82	$16.16	$15.30	$20.26	$15.73	$14.45	$16.95	$16.37	$15.94	$16.94	$16.38

Claim Counts	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Total Claim Count (FFS & Encounter)	1,058,103	1,039,266	1,056,030	1,088,617	1,032,760	1,090,696	1,070,848	1,010,246	1,162,754	1,133,771	1,122,968	1,159,518	1,085,465
Mental Health Carve-Out Drugs	174,471	171,634	173,404	177,441	174,286	186,760	182,961	172,860	197,237	187,121	184,044	191,595	181,151
FFS Physical Health Drugs	36,784	35,560	36,442	37,802	33,999	36,603	37,990	35,910	42,123	41,425	40,768	41,486	38,074
FFS Physician Administered Drugs	10,005	10,114	10,089	10,460	9,903	10,262	11,260	10,063	11,278	10,428	9,861	9,536	10,272
Encounter Physical Health Drugs	723,353	706,070	722,781	743,125	704,732	743,875	722,916	681,998	788,330	774,337	769,164	797,226	739,826
Encounter Physician Administered Drugs	113,490	115,888	113,314	119,789	109,840	113,196	115,721	109,415	123,786	120,460	119,131	119,675	116,142

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$85.50	$84.69	$84.01	$82.56	$83.62	$89.73	$87.20	$88.72	$90.60	$88.68	$87.05	$89.95	$86.86
Mental Health Carve-Out Drugs	$54.27	$53.46	$53.22	$53.26	$52.50	$53.91	$55.69	$59.01	$61.43	$62.82	$61.90	$62.91	$57.03
FFS Physical Health Drugs	$69.57	$66.70	$68.13	$68.11	$67.64	$70.91	$117.84	$115.75	$119.87	$114.67	$107.38	$116.27	$91.90
FFS Physician Administered Drugs	$157.41	$113.09	$108.94	$155.69	$127.80	$118.99	$133.33	$179.95	$141.36	$128.16	$116.70	$176.58	$138.17
Encounter Physical Health Drugs	$84.19	$84.05	$83.23	$80.71	$82.49	$84.79	$84.08	$85.24	$86.83	$84.01	$82.58	$84.22	$83.87
Encounter Physician Administered Drugs	$140.67	$137.86	$138.99	$135.64	$141.16	$184.72	$141.97	$140.15	$146.49	$146.51	$145.35	$155.32	$146.24

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$20.31	$20.24	$20.58	$20.10	$20.76	$21.35	$23.41	$23.47	$23.03	$22.32	$21.88	$22.93	$21.70
Mental Health Carve-Out Drugs	$16.83	$16.79	$16.33	$16.35	$16.38	$16.55	$17.97	$17.97	$17.58	$17.26	$17.01	$17.04	$17.00
FFS Physical Health Drugs	$20.27	$20.57	$21.21	$21.14	$21.28	$22.62	$70.09	$70.62	$74.17	$73.44	$72.92	$78.60	$47.24
Encounter Physical Health Drugs	$21.24	$21.15	$21.69	$21.05	$21.94	$22.62	$22.65	$22.72	$22.05	$21.30	$20.90	$21.97	$21.77

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$556.57	$550.55	$510.39	$476.97	$507.89	$548.76	$552.09	$556.62	$549.98	$473.19	$427.63	$464.10	$514.56
Mental Health Carve-Out Drugs	$1,108.05	$1,104.82	$1,101.09	$1,104.96	$1,083.85	$1,098.66	$1,124.69	$1,108.35	$1,052.59	$1,031.04	$1,018.43	$1,013.79	$1,079.19
FFS Physical Health Drugs	$280.23	$274.94	$271.38	$261.68	$264.26	$281.88	$332.60	$304.33	$290.73	$235.56	$195.37	$228.16	$268.43
Encounter Physical Health Drugs	$540.90	$534.05	$490.88	$455.52	$488.06	$529.83	$528.68	$534.53	$531.08	$453.72	$409.54	$443.85	$495.05

Generic Drug Use Percentage	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Generic Drug Use Percentage	89.2%	89.2%	88.5%	88.0%	88.6%	89.2%	89.3%	89.1%	88.6%	86.9%	85.7%	86.7%	88.3%
Mental Health Carve-Out Drugs	96.6%	96.6%	96.6%	96.6%	96.6%	96.5%	96.6%	96.2%	95.8%	95.5%	95.5%	95.4%	96.2%
FFS Physical Health Drugs	81.0%	81.9%	81.2%	80.5%	80.9%	81.4%	81.8%	80.7%	78.9%	74.6%	71.9%	74.8%	79.1%
Encounter Physical Health Drugs	87.9%	87.7%	86.9%	86.3%	87.0%	87.7%	87.9%	87.8%	87.3%	85.5%	84.1%	85.2%	86.8%

Preferred Drug Use Percentage	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Avg Monthly
Preferred Drug Use Percentage	85.37%	85.29%	86.77%	86.68%	86.67%	86.65%	86.70%	86.60%	86.55%	89.70%	89.80%	89.70%	87.2%
Mental Health Carve-Out Drugs	72.83%	72.85%	77.40%	77.28%	77.16%	77.37%	77.24%	76.90%	76.90%	93.03%	93.05%	93.04%	80.4%
FFS Physical Health Drugs	94.22%	94.22%	94.69%	94.36%	94.28%	94.78%	94.41%	94.17%	94.20%	94.35%	94.38%	94.36%	94.4%
Encounter Physical Health Drugs	87.92%	87.85%	88.63%	88.57%	88.67%	88.58%	88.69%	88.66%	88.58%	88.67%	88.78%	88.66%	88.5%

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 20, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2021

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA*	Antipsychotics, 2nd Gen	$6,595,325	15.9%	5,474	$1,205	Y
2	INVEGA SUSTENNA*	Antipsychotics, Parenteral	$3,386,342	8.1%	1,581	$2,142	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,707,097	6.5%	2,392	$1,132	Y
4	STRATTERA*	ADHD Drugs	$2,614,033	6.3%	5,741	$455	Y
5	REXULTI*	Antipsychotics, 2nd Gen	$1,936,255	4.7%	1,732	$1,118	V
6	ABILIFY MAINTENA*	Antipsychotics, Parenteral	$1,813,330	4.4%	874	$2,075	Y
7	INVEGA TRINZA*	Antipsychotics, Parenteral	$906,187	2.2%	140	$6,473	Y
8	ARISTADA*	Antipsychotics, Parenteral	$783,215	1.9%	340	$2,304	Y
9	TRINTELLIX	Antidepressants	$720,348	1.7%	1,752	$411	V
10	INVEGA*	Antipsychotics, 2nd Gen	$719,297	1.7%	1,740	$413	V
11	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$571,282	1.4%	630	$907	Y
12	SERTRALINE HCL	Antidepressants	$554,378	1.3%	55,914	$10	Y
13	VIIBRYD	Antidepressants	$503,119	1.2%	1,655	$304	V
14	BUPROPION XL	Antidepressants	$502,386	1.2%	37,201	$14	Y
15	DULOXETINE HCL	Antidepressants	$499,899	1.2%	35,055	$14	Y
16	FLUOXETINE HCL	Antidepressants	$449,131	1.1%	40,649	$11	Y
17	TRAZODONE HCL	Antidepressants	$447,466	1.1%	44,804	$10	
18	ESCITALOPRAM OXALATE	Antidepressants	$368,132	0.9%	37,492	$10	Y
19	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$303,545	0.7%	24,331	$12	
20	LAMOTRIGINE	Antiepileptics (non-injectable)	$299,565	0.7%	27,697	$11	Y
21	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$273,032	0.7%	2	$136,516	
22	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$255,483	0.6%	23	$11,108	Y
23	CHOLBAM*	Bile Therapy	$248,984	0.6%	6	$41,497	N
24	Inj Pembrolizumab	Physican Administered Drug	$233,737	0.6%	50	$4,675	
25	VENLAFAXINE HCL ER	Antidepressants	$228,885	0.6%	18,194	$13	Y
26	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$227,861	0.5%	18,368	$12	Y
27	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$220,440	0.5%	2,850	$77	V
28	BIKTARVY	HIV	$219,419	0.5%	84	$2,612	Y
29	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$209,082	0.5%	18,883	$11	Y
30	BUPROPION XL	Antidepressants	$189,940	0.5%	1,010	$188	V
31	CITALOPRAM HBR	Antidepressants	$178,201	0.4%	20,602	$9	Y
32	AMITRIPTYLINE HCL*	Antidepressants	$176,030	0.4%	13,888	$13	Y
33	VENLAFAXINE HCL ER	Antidepressants	$175,806	0.4%	2,152	$82	V
34	SPRAVATO*	Antidepressants	$171,325	0.4%	141	$1,215	V
35	LAMICTAL ODT	Antiepileptics (non-injectable)	$169,586	0.4%	187	$907	V
36	TRIKAFTA*	Cystic Fibrosis	$162,959	0.4%	19	$8,577	N
37	CAPLYTA*	Antipsychotics, 2nd Gen	$162,369	0.4%	119	$1,364	V
38	MIRTAZAPINE	Antidepressants	$155,803	0.4%	10,903	$14	Y
39	WELLBUTRIN XL	Antidepressants	$155,361	0.4%	195	$797	Y
40	OLANZAPINE*	Antipsychotics, 2nd Gen	$150,048	0.4%	11,979	$13	Y
		Top 40 Aggregate:	**$30,644,681**		**446,849**	**$5,718**	
		All FFS Drugs Totals:	**$41,567,127**		**670,839**	**$611**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: January 20, 2022

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2021

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$273,032	3.0%	2	$136,516	
2	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$255,483	2.8%	23	$11,108	Y
3	CHOLBAM*	Bile Therapy	$248,984	2.8%	6	$41,497	N
4	Inj Pembrolizumab	Physican Administered Drug	$233,737	2.6%	50	$4,675	
5	BIKTARVY	HIV	$219,419	2.4%	84	$2,612	Y
6	TRIKAFTA*	Cystic Fibrosis	$162,959	1.8%	19	$8,577	N
7	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$145,589	1.6%	5	$29,118	
8	CONCERTA*	ADHD Drugs	$139,557	1.6%	411	$340	N
9	IBRANCE*	Antineoplastics, Newer	$133,373	1.5%	12	$11,114	
10	LANTUS SOLOSTAR*	Diabetes, Insulins	$129,746	1.4%	393	$330	Y
11	SABRIL	Antiepileptics (non-injectable)	$127,169	1.4%	6	$21,195	N
12	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$124,726	1.4%	224	$557	Y
13	VIMPAT	Antiepileptics (non-injectable)	$118,272	1.3%	218	$543	Y
14	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$115,369	1.3%	394	$293	
15	HUMIRA(CF) PEN*	Targeted Immune Modulators	$112,781	1.3%	37	$3,048	Y
16	REVLIMID	STC 30 - Antineoplastic	$106,115	1.2%	7	$15,159	
17	Etonogestrel Implant System	Physican Administered Drug	$104,038	1.2%	151	$689	
18	VYVANSE*	ADHD Drugs	$102,772	1.1%	597	$172	Y
19	ELIQUIS	Anticoagulants, Oral and SQ	$98,605	1.1%	273	$361	Y
20	PFIZER COVID-19 VACCINE (EUA)	STC 90 - Biologicals	$95,843	1.1%	2,410	$40	
21	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$92,275	1.0%	2,357	$39	Y
22	DARAPRIM	STC 32 - Antimalarials	$89,996	1.0%	2	$44,998	
23	AFINITOR DISPERZ*	Antineoplastics, Newer	$85,555	1.0%	8	$10,694	
24	Aflibercept Injection	Physican Administered Drug	$83,454	0.9%	162	$515	
25	STELARA*	Targeted Immune Modulators	$82,425	0.9%	17	$4,849	N
26	Mirena, 52 Mg	Physican Administered Drug	$80,373	0.9%	115	$699	
27	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$74,071	0.8%	7	$10,582	N
28	ENBREL SURECLICK*	Targeted Immune Modulators	$72,369	0.8%	18	$4,021	Y
29	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$71,432	0.8%	5	$14,286	
30	NORDITROPIN FLEXPRO*	Growth Hormones	$68,528	0.8%	27	$2,538	Y
31	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$68,093	0.8%	1,208	$56	Y
32	FLOVENT HFA	Corticosteroids, Inhaled	$61,840	0.7%	427	$145	Y
33	DEMSER	STC 71 - Other Hypotensives	$58,598	0.7%	1	$58,598	
34	Inj. Pemetrexed Nos 10mg	Physican Administered Drug	$56,994	0.6%	32	$1,781	
35	MODERNA COVID-19 VACCINE (EUA	STC 90 - Biologicals	$56,593	0.6%	1,454	$39	
36	Pertuzu, Trastuzu, 10 Mg	Physican Administered Drug	$55,510	0.6%	4	$13,877	
37	EPIDIOLEX*	Antiepileptics (non-injectable)	$53,142	0.6%	60	$886	N
38	PROMACTA	Thrombocytopenia Drugs	$50,992	0.6%	12	$4,249	Y
39	Infliximab Not Biosimil 10mg	Physican Administered Drug	$50,120	0.6%	39	$1,285	
40	JYNARQUE	STC 79 - Diuretics	$48,259	0.5%	3	$16,086	
		Top 40 Aggregate:	**$4,408,188**		**11,280**	**$11,954**	
		All FFS Drugs Totals:	**$8,980,782**		**109,594**	**$623**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: January 20, 2022

ProDUR Report for October through December 2021
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	3	1	0	2	0.00%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,665	529	0	2,136	1.75%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	7,738	1,883	0	5,855	5.08%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	98,814	16,891	23	81,896	64.90%	**17.1%**
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	31,149	7,287	4	17,854	20.46%	**N/A**
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	805	118	0	687	0.53%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	1	1	0	0	0.00%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	880	237	0	643	0.58%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	451	142	0	309	0.30%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	24	21	0	3	0.02%	**87.5%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	9,717	2,565	0	7,149	6.38%	**N/A**
		Totals	**152,247**	**29,675**	**27**	**116,534**	**100.00%**	**19.5%**

ProDUR Report for October through December 2021

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	2,070	318	1,752	15,675	13.3%	15.4%
ER	Lorazepam	406	119	286	13,030	3.1%	29.3%
ER	Alprazolam	240	53	187	7,981	3.1%	22.1%
ER	Diazepam	125	27	98	4,544	2.9%	21.6%
ER	Buspar (Buspirone)	3,635	514	3,121	34,856	10.6%	14.4%
ER	Lamictal (Lamotrigine)	6,458	1,182	5,276	46,843	14.1%	18.3%
ER	Seroquel (Quetiapine)	4,801	925	3,876	32,601	15.1%	19.3%
ER	Zyprexa (Olanzapine)	2,751	583	2,167	20,345	13.7%	21.2%
ER	Risperdal (Risperidone)	2,100	388	1,712	14,765	14.4%	18.5%
ER	Abilify (Aripiprazole)	3,834	586	3,248	29,059	13.4%	15.3%
ER	Wellbutrin (Bupropion)	7,254	1,070	6,184	74,306	9.9%	14.8%
ER	Suboxone (Buprenorphine/Naloxone)	96	41	55	1,941	5.0%	42.7%
ER	Zoloft (Sertraline)	8,350	1,344	7,006	80,553	10.5%	16.1%
ER	Prozac (Fluoxetine)	5,687	871	4,816	57,357	10.2%	15.3%
ER	Lexapro (Escitalopram)	5,471	826	4,644	53,807	10.4%	15.1%
ER	Celexa (Citalopram)	2,512	336	2,176	28,172	8.9%	13.4%
ER	Trazodone	7,016	1,132	5,884	62,714	11.4%	16.1%
ER	Cymbalta (Duloxetine)	5,243	836	4,407	49,377	10.9%	15.9%
ER	Intuniv (Guanfacine)	1,950	238	1,700	14,814	13.7%	12.2%

ProDUR Report for October through December 2021

Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	October	5,734	84	289	800	6	2,509	109	0	159
ER	November	6,223	151	286	882	4	2,789	185	0	185
ER	December	4,934	130	203	609	8	2,389	141	0	136
	Total =	**16,891**	**365**	**778**	**2,291**	**18**	**7,687**	**435**	**0**	**480**
	Percentage of Total Overrides =		**2.2%**	**4.6%**	**13.6%**	**0.1%**	**45.5%**	**2.6%**	**0.0%**	**2.8%**

ProDUR Report for October through December 2021			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
	DA	2	$429.98
Oct-21	DC	8	$1,930.04
Oct-21	DD	25	$3,930.88
Oct-21	ER	331	$69,426.01
Oct-21	HD	10	$978.10
Oct-21	ID	44	$6,559.75
Oct-21	LD	1	$484.48
Oct-21	PG	27	$4,392.16
Oct-21	TD	16	$3,680.97
		October Savings =	**$91,812.37**
Nov-21	DD	2	$29.61
Nov-21	ER	46	$14,275.51
Nov-21	HD	1	$34.99
Nov-21	ID	17	$6,623.57
Nov-21	LR	1	$159.49
Nov-21	MX	1	$36.99
Nov-21	TD	2	$2,347.54
		November Savings =	**$23,507.70**
Dec-21	DC	1	$65.99
Dec-21	DD	4	$605.75
Dec-21	ER	57	$15,931.54
Dec-21	HD	1	$0.01
Dec-21	ID	14	$2,340.97
Dec-21	TD	4	$3,193.88
		December Savings =	**$22,138.14**
		Total 4Q2021 Savings =	**$137,458.21**

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	61	15		
		Unique Patients Identified	62	15		
		Total Faxes Successfully Sent	45	12		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	24	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$11,217	$254		
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	191	28		
		Unique Patients Identified	193	29		
		Total Faxes Successfully Sent	133	21		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	73	2		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$11,422	$179		

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	30			
		Total Faxes Successfully Sent	9			
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	3			
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6			
		Safety Monitoring Profiles Identified	1			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$1,214			

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	801			
		High risk patients identified	9			
		Prescribers successfully notified	2			
		Patients with continued antipsychotic therapy in the following 90 days	1			
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	81	6		
		Total prescribers identified	80	6		
		Prescribers successfully notified	80			
		Patients with claims for the same antipsychotic within the next 90 days	32			
		Patients with claims for a different antipsychotic within the next 90 days	5			

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR_Profiles Reviewed	5			
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	2			
	Children in foster care under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	19			
	High Risk Patients - Bipolar	RetroDUR_Profiles Reviewed	13			
		RetroDUR_Letters Sent To Providers	9			
	High Risk Patients - Mental Health	RetroDUR_Profiles Reviewed	50			
		RetroDUR_Letters Sent To Providers	64			
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed	16			
		RetroDUR_Letters Sent To Providers	11			
	Lock-In	RetroDUR_Profiles Reviewed	20			
		RetroDUR_Letters Sent To Providers	4			
		Locked In	3			
	Polypharmacy	RetroDUR_Profiles Reviewed	1			

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	90	8		
		Total prescribers identified	90	8		
		Prescribers successfully notified	90			
		Patients with discontinuation of therapy within next 90 days	39	8		
		Average number of sedative drugs dispensed within next 90 days	14	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	14	0		
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified	79	9		
		Patients with a paid claim for the drug (based on HSN) within 14 days	52			
		Patients without a paid claim within 14 days	13			
	ICS/LABA	ICS/LABA Denials	15	2		
		Disqualified	4			
		Faxes Sent	1			
		No Subsequent Pulmonary Claims	1			
	Oncology Denials	Total patients identified	1			
		Total prescribers identified	1			
		Prescribers successfully notified	1			
		Patients with claims for the same drug within the next 90 days	1			
		Patients with claims for any oncology agent within the next 90 days	1			

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2021 - 2022

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	TCAs in Children	TCA Denials in Children	27	5		
		Total patients identified	6	3		
		Total prescribers identified	6	3		
		Prescribers successfully notified	3			
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days	1			

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
August 2021 Volume 11 Issue 6

Therapeutic Uses for Cannabinoids

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group

Cannabis (e.g., hemp, marijuana) and synthetic cannabinoids have a long history of therapeutic, as well as recreational, uses. While over 100 different cannabinoids have been isolated from cannabis, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most well-known.[1] Many patients request information from providers on the benefits and risks of cannabinoid products. This newsletter will present the evidence for potential uses of THC and CBD products as well as legal restrictions, drug interactions and safety precautions.

Cannabinoid Legal Implications

There are several factors that determine the regulations that apply to cannabinoid products. Hemp-derived products are not considered federally controlled substances if they contain 0.3% or less of THC (by dry weight).[1] CBD products from hemp can be used in cosmetics and some states allow consumable CBD products. Laws governing the use of cannabinoids depends on the state in which you live and the plant that was the basis of the product (hemp vs. marijuana). The product may require a prescription or be available online or at a dispensary or smoke shop. In Oregon, individuals 21 years or older can purchase up to one ounce of cannabis. The Oregon Medical Marijuana Act also allows for the use of marijuana for conditions listed in **Table 1**.[2] Patients that qualify for a medical marijuana may pay lower costs, be able to purchase more potent products and grow additional plants compared to those individuals using marijuana for recreational purposes only. At this time medical cannabis may only be authorized by an Oregon licensed Doctor of Medicine (MD) or Doctor of Osteopathic Medicine (DO).

Table 1. Qualifying Medical Marijuana Uses in Oregon.[2]

• Cancer	• Glaucoma
• Degenerative or pervasive neurological condition	• HIV/AIDs
• Medical condition or treatment for a medical condition that produces one or more of the following: Cachexia, severe pain, severe nausea, seizures and persistent muscle spams	• Post-traumatic stress disorder (PTSD)

Cannabinoid Pharmacology

CBD and THC have unique targets and therapeutic effects due to a non-enzymatic decarboxylation process that results in differing chemical structures.[3] Decarboxylation activates raw cannabis into active forms and can be done through heat or vaporization. THC activates CB 1 receptors in the brain which results in psychoactive effects, which are not associated with CBD. CBD has numerous putative biological targets and has been proposed to act as a negative allosteric modulator of cannabinoid receptors.[4] Lack of quality control and unknown bioavailability of cannabinoid products complicate the predictability of pharmacological effects of non-Food and Drug Administration (FDA) approved products (e.g., edibles, vapors, purified liquids).

Therapeutic Effects of Cannabinoids

Cannabinoids are anecdotally used for a multitude of ailments (e.g., muscle relaxant, analgesia, appetite stimulation). There are only three FDA-approved products. The THC-based synthetic product, dronabinol (Marinol®, Syndros®), is approved for use in adults for anorexia associated with weight loss in patients with Acquired Immunodeficiency Syndrome (AIDS) and nausea and vomiting associated with cancer chemotherapy for patients who have failed standard antiemetic regimens.[5] The third approved product is a CBD derivative, cannabidiol (Epidiolex®), approved for patients aged 1 year or older for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex.[6]

The therapeutic effects of cannabinoids, vary between products and routes of administration. Food may cause erratic absorption of CBD and edible CBD products (e.g., gummy bears, brownies) are associated with the least predictable absorption profiles.[7] Liquid formulations are more predictable with maximum concentrations reported at 3-5 hours after ingestion. Products that are oil based have the best absorption as cannabis is lipophilic. Vaping has the quickest onset of action with maximum concentrations seen at 15-30 minutes.[7] The time it takes to metabolize cannabis is also variable. Most urine drug screens test for THC or its metabolites. Tests may remain positive after a week to 10 days after use and up to 6 weeks if the patient is a heavy user.[1] CBD and hemp oil do not usually cause a positive test due to low levels of THC. Rarely CBD may cause a positive test with use of impure forms or very high doses.[1]

Evidence Supporting the Use of Cannabinoids

There is a lack of evidence to draw strong conclusions on efficacy for the medicinal use of most cannabinoid products, especially those which are not FDA approved. There is limited evidence, beyond anecdotal, to support the use of CBD and THC for some indications (**Table 2**). The majority

of evidence is low-quality and there is a need for randomized clinical trials to determine true effects of treatment. Federal restrictions present a barrier to conducting research in a formalized manner. The National Institute on Drug Abuse (NIDA) has adopted a policy to guide researchers to measure and report findings on cannabis using a standard THC unit of 5 mg. This recommendation does not limit use to 5 mg but rather standardizes the comparable effects of THC.[8] Additional challenges to the use of cannabinoids are the lack of consistency between different dosage forms and potency.

Table 2. Cannabinoid Uses with Limited Evidence.

Condition	Evidence	Strength of Evidence
CBD (oral)		
• Psychotic episodes in patients with Parkinson's disease	Small, non-controlled study (n=6) lasting 4 weeks demonstrated reductions in BPRS and PPQ with CBD 150 mg/day, compared to baseline levels[9]	Low
• Anxiety associated with public speaking	Small study (n=24) randomized patients to CBD 600 mg/day or placebo demonstrated reductions in anxiety, cognitive impairment, discomfort and alert levels with CBD[10]	Low
• Anxiety	Small study (n=72) demonstrated anxiety score reduction in 79% of patients in the first month[11]	Low
• Refractory seizures in patients with Dravet syndrome	- FDA-approved (Epidiolex®; Schedule V) - PC trial of 120 children and young adults with Dravet syndrome (baseline seizure rate of 14/month) received oral CBD 20 mg/kg which decreased conclusive seizures by 22.8% (95% CI, -41.1 to -5.4; P=0.01) more than placebo[12]	Low
• Refractory seizures in patients with Lennox-Gastaut syndrome	- FDA-approved (Epidiolex®) - PC trial of 171 patients (age 2-55 years, baseline seizure frequency of 74/month) with Lennox-Gastaut syndrome received oral CBD 20 mg/kg as add on therapy which decreased monthly drop seizure frequency by 17.21% (95% CI, -30.32 to -4.09; P=0.0135) more than placebo compared to baseline[13]	Low
THC (oral)		
• Refractory chemotherapy -induced nausea and vomiting	- FDA-approved (Marinol® capsules; Schedule III) - FDA-approved (Syndros® solution; Schedule II) - Meta-analysis of 6462 patients demonstrated a complete response with cannabinoids in 47% of patients compared to 20% with placebo (OR 3.82; 95% CI, 1.55 to 9.42: P < 0.05)	Low
THC (oral or inhaled)		
• Appetite stimulant in patients with HIV or AIDs	- FDA-approved (Marinol®; Schedule III)[5] - FDA-approved (Syndros® solution; Schedule II) Study in 139 patients showed an improvement of 9 points on a visual analog scale compared to placebo (p<0.05) for the outcome of improvement in appetite	Low
• Refractory chronic pain	Plant derived cannabinoids were found to reduce pain 40% more than control	Low

	(OR 1.41, 95% CI, 0.99 to 2.00); results not SS (pooled analysis of 7 trials, n=178)[14]	
• Symptom Improvement in: - Tourette syndrome - PTSD	Limited to case reports and anecdotal evidence[1,7]	Low

Abbreviations: AIDS – Acquired Immunodeficiency Syndrome; BPRS – Brief Psychiatric Rating Scale; CBD – cannabidiol; CI – confidence interval; HIV – Human Immunodeficiency Syndrome; FDA – Food and Drug Administration; OR – odds ratio; PC – placebo-controlled; PPQ – Personal Problems Questionnaire; PTSD – post-traumatic stress disorder; RCT – randomized controlled trial; SS – statistically significant; THC - Δ-9-tetrahydrocannabinol

Adverse Events Associated with Cannabinoids

The use of cannabinoids commonly results in adverse events, with an incidence rate of approximately 50%.[7] Adverse events are more commonly seen with higher doses and prolonged use.[7] CBD may cause decreased appetite and weight loss, diarrhea, dizziness, drowsiness, sleep disturbance, abnormal liver enzymes and fatigue.[7;1] Liver injury at higher doses (e.g., 20 mg/kg/day) or when used in combination with clobazam or valproate has also been reported with CBD use.[1] THC has been associated with euphoria, hyperemesis syndrome and psychoactive effects (e.g., dizziness, sedation, disorientation, dissociation, paranoia, euphoric mood, feeling drunk and disturbances in attention).[7] A systematic review and meta-analysis found that cannabis use in adolescents, 18 years of age and under, resulted in increased risk of depression and suicidality; however, additional high-quality studies are needed to substantiate findings.[15] Findings from the use of rimonabant, an inverse agonist of the cannabinoid receptor used for weight-loss, resulted in withdrawal from the European market due to serious psychiatric adverse effects (this product was never approved in the United States).[16]

Cannabinoid Drug Interactions

Cannabinoids are metabolized by numerous metabolic systems which have the potential to cause multiple drug interactions (**Table 3**). The Cytochrome P-450 enzymes systems, 3A4, 2C9, 2C19, 2D6 and 1A2 are responsible for the metabolism of both THC and CBD.[7] CBD is also metabolized by secondary metabolic pathways and transport proteins (e.g., UGT1A9, UGT2B7, BCRP, BSEP), with the potential to increase adverse effects of the substrate medication.[7] THC has demonstrated the potential to displace highly protein bound drugs which can increase drug levels and increase the risk of toxicity.[1] THC may also produce an additive effect when used in combination with hypnotics, sedatives, psychotropics and alcohol.

Table 3. CBD and THC Drug Interactions[1]

Enzyme	Drug Characteristic	Recommendation	Example Drugs*
Cannabidiol (CBD)			
CYP3A4	Moderate to Strong Inhibitors	Reduce CBD dose	ritonavir, verapamil, voriconazole
CYP2C19	Moderate to Strong Inhibitors	Reduce CBD dose	fluconazole, omeprazole
CYP3A4	Inducers	Consider increasing CBD dose	carbamazepine, St. John's wort
CYP2C19	Inducers	Consider increasing CBD dose	primidone, rifampin
CYP2C8	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	amiodarone, carbamazepine, warfarin
CYP2C9	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	amitriptyline, phenytoin
CYP2C19	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	clobazam (active metabolite), citalopram, clopidogrel, phenytoin, valproic acid
Delta-9-tetrahydrocannabinol (THC)			
CYP2C9	Inhibitors	Consider reducing THC dose	ginkgo, sulfamethoxazole
CYP3A4	Inhibitors	Consider reducing THC dose	ritonavir, verapamil, voriconazole
CYP2C9	Inducers	Consider increasing THC dose	carbamazepine, phenytoin
CYP3A4	Inducers	Consider increasing THC dose	carbamazepine, St. John's wort

Abbreviations: CBD – cannabidiol; THC - Δ-9-tetrahydrocannabinol
Key: * Interaction potential for all drugs that utilize that enzyme system

- Marinol, Syndros and Epidiolex require prior authorization for OHA Fee-For-Service patients
- OHP patients qualify for a reduced medical marijuana card fee

Cannabis products may have a role in the management of medical ailments. Multiple dosage routes, unknown composition and varying costs complicate the use of non-

approved products. Additionally, there are few high quality studies to guide expected outcomes and adverse events. Patients should be made aware of potential drug interactions and adverse reactions associated with both CBD and THC products.

Peer Reviewed By: Tracy Klein, PhD, ARNP, Washington State University, Vancouver, Washington and Jane Ishmael, PhD, Associate Professor, Oregon State University College of Pharmacy, Corvallis, Oregon

References:

1. Clinical Resource, Comparison of Cannabinoids. *Pharmacist's Letter/Prescriber's Letter*. September 2018.
2. Oregon Health Authority. Qualifying Medical Conditions for Medical Marijuana. Available at: https://www.oregon.gov/oha/PH/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/Physicians.aspx#role. Accessed June 29, 2021.
3. Britch SC, Babalonis S, Walsh SL. Cannabidiol: pharmacology and therapeutic targets. *Psychopharmacology (Berl)*. 2021;238(1):9-28. doi:10.1007/s00213-020-05712-8
4. Laprairie, RB, Bagher AM, Kelly MEM,, Denovan-Wright EM. Cannabidiol is a Negative Allosteric Modulator of the Cannabinoid CB1 Receptor. *British Journal of Pharmacology*. 2015;172:4790-4805.
5. Marinol (dronabinol) [prescribing information]. North Chicago, IL, AbbVie Inc. August 2017.
6. Epidiolex (cannabidiol) [prescribing information]. Carlsbad, CA, Greenwich Biosciences, Inc. October 2020.
7. Brown JD, Winterstein AG. Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. *J Clin Med*. 2019;8(7):E989. doi:10.3390/jcm8070989.
8. Valkow, N, Sharpless, N. Establishing 5 mg THC as the Standard Unit for Research. National Institute on Drug Abuse. May 2021. Available at: www.drugabuse.gov. Accessed August 5, 2021.
9. Zuardi AW, Crippa J, Hallak J, et al. Cannabidiol for the Treatment of Psychosis in Parkinson's disease. *Hospital Pharmacy*. 2009;23(8):979-983.
10. Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol Reduces the Anxiety induced by Simulated Public Speaking in Treatment-naïve Social Phobia Patients. *Neuropsychopharmacology*. 2011;36(6):1219-1226. doi:10.1038/npp.2011.6.
11. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J*. 2019;23:18-041. doi:10.7812/TPP/18-041.
12. Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376(21):2011-2020. doi:10.1056/NEJMoa1611618.
13. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391(10125):1085-1096. doi:10.1016/S0140-6736(18)30136-3.
14. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. *National Academies Press* (US); 2017. Accessed July 6, 2021. http://www.ncbi.nlm.nih.gov/books/NBK423845/.
15. Gobbi G, Atkin T, Zytynski T, et al. Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2019;76(4):426-434. doi:10.1001/jamapsychiatry.2018.4500.
16. Topol EJ, Bousser M-G, Fox KAA, et al. Rimonabant for Prevention of Cardiovascular Events (CRESCENDO): a Randomised, Multicentre, Placebo-controlled Trial. *Lancet*. 2010;376(9740):517-523. doi:10.1016/S0140-6736(10)60935-X..

Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy Sentena
sentenak@ohsu.edu

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
September 2021 Volume 11 Issue 7

Updates in Heart Failure Therapy: New Drugs and Indications

Kelli Hoang, Pharm.D. Candidate 2022, Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management Group

Heart failure (HF) is a structural or functional cardiac disorder resulting in reduced cardiac output and/or elevated cardiac pressures. In the United States, about 6.2 million adults have HF, and the prevalence is expected to increase to over 8 million adults by 2030.[1,2] It is further classified into HF with reduced ejection fraction (HFrEF = left ventricular ejection fraction ≤ 40%) and HF with preserved ejection fraction (HFpEF = left ventricular ejection fraction ≥ 50%). Until recently, guideline directed medication therapy (GDMT), including select renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs), are the only medications that have demonstrated a mortality benefit in HFrEF.[3] The purpose of this newsletter is to review evidence on cardiovascular (CV) outcomes for expanded indications (**Table 1**) of sacubitril/valsartan, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and the recently FDA-approved vericiguat.

Table 1. New or Expanded Heart Failure Indications

Drug	Adult Heart Failure Indications	Target Dose
Vericiguat[4]	To reduce risk of CV death & HF hospitalization following a HF hospitalization or IV diuretic use in HFrEF	10 mg once daily
Sacubutril/ Valsartan[5]	To reduce risk of CV death & HF hospitalization in chronic HF. Benefits most evident if LVEF is below normal.	97 mg/ 103 mg twice daily
Dapagliflozin[6]	To reduce risk of CV death and HF hospitalization in adults with HFrEF	10 mg once daily

Abbreviations: CV – cardiovascular; HF- heart failure, HFrEF – heart failure with reduced ejection fraction; LVEF- left ventricular ejection fraction; mg - milligram

Vericiguat: New Heart Failure Medication

Vericiguat is a soluble guanylate cyclase (sGC) stimulator, causing vasodilation through the nitric oxide pathway.[4] Common side effects include hypotension and anemia. It is contraindicated with concurrent use of long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors and in pregnancy.[4]

Approval was based on the VICTORIA trial (**Table 2 and 3**), a placebo-controlled, multicenter, double-blind, randomized controlled trial (RCT) that compared vericiguat to matching placebo in patients with HFrEF and on GDMT.[7] By the median follow-up of 10.8 months, a statistically significant reduction in CV death and HF hospitalizations occurred with vericiguat versus placebo (35.5% vs. 38.5%; hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.82 to 0.98; p = 0.02), primarily driven by HF hospitalizations (**Table 3**).[7] There was no significant reduction in CV death or all-cause mortality. Vericiguat should not be used for HFpEF. A 6-month study in HFpEF resulted in an increase of CV death with vericiguat 10 mg daily compared to placebo (4.6% vs. 1.5%, respectively) and did not improve physical functioning.[8]

The VICTORIA trial has limited generalizability since it enrolled a higher risk population of patients with worsening HF, defined as hospitalization within the previous 6 months or use of intravenous (IV) diuretics within 3 months.[7] This resulted in a study population with more advanced HF. Sixty seven percent of patients had a recent HF hospitalization and 41% of patients had NYHA Class III or IV, compared to 29-33% in other landmark HF trials.[7, 9-12]

Vericiguat should be reserved as a last line, add-on treatment to optimized GDMT for patients with advanced, symptomatic HFrEF with a recent decompensation.[7] Moderate quality evidence suggests that for this population, vericiguat reduces HF hospitalization and CV death but does not reduce overall mortality.[7]

Table 2. Summary of Recent Heart Failure Trials

Trial	Treatment Arms	Population	Mean Baseline LVEF
PARADIGM HF[9]	Sacubitril/Valsartan vs. Enalapril	HFrEF (EF ≤ 35%)	30%
PARAGON HF[10]	Sacubitril/Valsartan vs. Valsartan	HFpEF (EF ≥ 45%)	58%
VICTORIA[7]	Vericiguat vs. Placebo	Advanced HFrEF (EF ≤ 45%)	29%
DAPA HF[11]	Dapagliflozin Vs. Placebo	HFrEF (EF ≤ 40%)	31%
EMPEROR Reduced[12]	Empagliflozin Vs. Placebo	HFrEF (EF ≤ 40%)	28%

Abbreviations: EF: ejection fraction; HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction

Sacubitril/Valsartan: Expanded Indication

Sacubitril/valsartan was previously approved for use in HFrEF, based on the PARADIGM-HF trial (**Table 2**).[5,9] In February 2021, the FDA labeling was expanded to include all adult patients with HF regardless of EF.[5] The expansion was based on PARAGON-HF, an active-control, double-

blind, RCT study (**Table 2**). Patients with symptomatic HFpEF who tolerated sacubitril/valsartan in an initial run-in period were randomized to a target dose of either valsartan 160 mg twice daily or sacubitril/valsartan 97/103 mg twice daily with median follow-up of 35 months.[10]

Overall, there was no statistical difference between sacubitril/valsartan and valsartan for the primary composite outcome of CV deaths and HF hospitalization (12.8 events per 100 patient years vs. 14.6; risk ratio [RR] 0.87; 95% CI 0.75 to 1.01; p=0.06).[10] HF hospitalizations were the primary driver of this outcome. Greater benefit was shown for the prespecified subgroup of patients with LVEF below the median of ≤ 57% (RR 0.78; 95% CI 0.64-0.95) than patients with LVEF above the median (RR 1.00; 95% CI 0.81-1.23).[10]

Despite failing to meet the primary outcome, the FDA expanded approval based on a re-analysis of the data.[13] The re-analysis found a statistically significant benefit (RR 0.84; 95% CI 0.74 to 0.97; p=0.014) after the composite endpoint was expanded to include HF urgent care visits and reexamination of unconfirmed HF hospitalizations.[13]

Sacubitril/valsartan's benefits remain most evident when EF is markedly reduced (≤40%) and should be used judiciously with higher baseline EF. Although expert consensus guidelines consider initiating sacubitril/valsartan without prior exposure to an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), a trial of an ACEI or ARB prior to initiation is a recommended strategy by the National Institute for Health and Care Excellence (NICE).[14, 15] This is also supported by pivotal trials, which used extensive run-in periods that excluded patients who could not tolerate RAAS inhibitors.[9,10] In PARADIGM-HF, over 20% of patients were unable to tolerate target doses and it is unclear if lower doses have any clinic benefit in HFrEF.

Table 3. Cardiovascular Outcome Results in HFrEF[7,9,11,12]

	CV death & HF hospitalization ARR/NNT	All-cause mortality ARR/NNT	CV Death ARR/NNT
Sacubitril/Valsartan*	4.7% / 22	2.8% / 36	3.2% / 32
Vericiguat ±	3.0% / 34	NS	NS
Dapagliflozin ±	4.9% / 21	2.3% / 44	1.9% / 53
Empagliflozin±	5.3% / 19	NS	NS

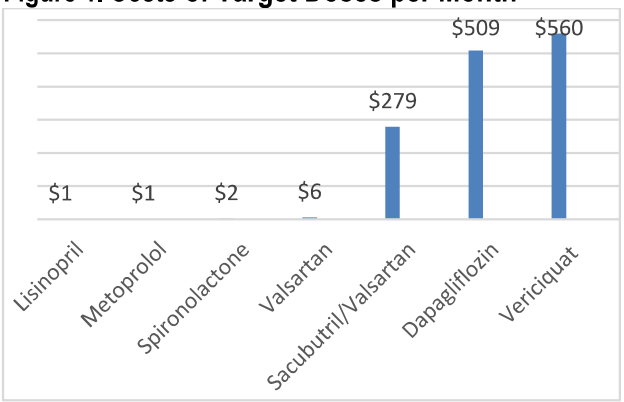
Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; HF: heart failure; NNT: number needed to treat; NS: not significant
*Active comparator: enalapril. ± Versus placebo

Updates to SGLT2 Inhibitor Use in Heart Failure

SGLT2 inhibitors have been shown to reduce HF hospitalizations in patients with diabetes and CV disease.[16,17] More recent data suggests empagliflozin and dapagliflozin may benefit patients with heart failure, with or without diabetes. Dapagliflozin was FDA approved for HFrEF based on the DAPA-HF trial (**Table 2 and 3**), demonstrating a reduction in worsening HF (defined by hospitalization or requiring intravenous therapy for HF) or CV death (HR 0.74; 95% CI; 0.65 to 0.85; p<0.001) with dapagliflozin compared to placebo in patients with HFrEF, with or without type 2 diabetes (T2D).[11] As of January 2021, empagliflozin is under FDA review for patients with HFrEF based on the EMPEROR-Reduced trial (**Table 2 and 3**).[12]

Based on these data, dapagliflozin is an add-on option to optimized GDMT (RAAS inhibitor, beta blocker, and an MRA) for treatment of symptomatic chronic HFrEF in adults.[18] No direct comparisons between dapagliflozin and other drugs have been made. When used with diuretic therapy, patients should be counseled on the risks of hypovolemia and acute kidney injury when initiated.

Figure 1. Costs of Target Doses per Month



*Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC).
**Vericiguat cost based on Average Wholesale Cost (AWP) minus 20% AAAC.

Conclusion

New drugs and indications provide additional options for patients with HF who remain symptomatic while on GDMT. However, very few patients are on GDMT at target doses. Attempts to optimize these cost-effective treatments (**Figure 1**) and address barriers to adherence should happen before adding on additional medications to already complex drug regimens.

For Oregon Health Plan (OHP) Fee-For Service (FFS):

- Sacubitril/valsartan and vericiguat require prior authorization (PA).
- Trial and failure with ACE-I/ARB is required to confirm tolerance.
- For HFrEF, optimization of an ACE-I/ARB and target dose beta blocker should be prioritized before adding additional therapies.
- Vericiguat should not be used for HFpEF or in less severe HFrEF
- SGLT2 inhibitor use should be prioritized for patients with HFrEF and T2D.

Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy Sentena
sentenak@ohsu.edu

Peer reviewed by: John Mackay, Pharm.D., BCPS, Clinical Pharmacist, Advanced Heart Failure and Heart Transplant, Providence Medical Group and Maurice N. Tran, Pharm.D., PGY-2 Pharmacy Resident, Ambulatory Care, Providence Medical Group

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. Mar 3 2020;141(9):e139-e596. doi:10.1161/cir.0000000000000757
2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the Impact of Heart Failure in the United States. *Circulation: Heart Failure*. 2013;6(3):606-619. doi:10.1161/HHF.0b013e318291329a
3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Circulation*. 2013;128(16):e240-e327. doi:10.1161/CIR.0b013e31829e8776
4. VERQUVO (vericiguat) [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc. January 2021.
5. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, February 2021.
6. FARXIGA (dapagliflozin) [prescribing information]. Willington, DE. AstraZeneca Pharmaceuticals LP. April 2021.
7. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*. 2020;382(20):1883-1893. doi:10.1056/NEJMoa1915928
8. Armstrong PW, Lam CSP, Anstrom KJ, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. *Jama*. Oct 20 2020;324(15):1512-1521. doi:10.1001/jama.2020.15922
9. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *New England Journal of Medicine*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
10. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *New England Journal of Medicine*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655
11. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303
12. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190
13. Entresto (sacubitril/valsartan) New Indication Approval Letter. February 2021. Center for Drug Evaluation and Research, Food and Drug Administration. U.S. Department of Health and Human Services. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/207620Orig1s018.pdf.
14. Maddox TM, Januzzi JL, Jr., Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. Feb 16 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022
15. Chesters C, Hay N, Farrar L, Yates S. Sacubitril/valsartan for Treating Symptomatic Chronic Heart Failure with Reduced Ejection Fraction: Guidance. NICE: The National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta388. Published April 27, 2016. Accessed July 22, 2021.
16. Salah HM, Al'Aref SJ, Khan MS, et al. Effect of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular and Kidney Outcomes-Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. *Am Heart J*. Feb 2021;232:10-22. doi:10.1016/j.ahj.2020.10.064
17. Cardoso R, Graffunder FP, Ternes CMP, Fernandes G, Rocha AV, Bhatt D. SGLT2 Inhibitor Therapy Reduces Mortality, Hospitalizations Across HF Subgroups: A Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*. 2021;77(18_Supplement_1):655-655. doi:10.1016/S0735-1097(21)02014-3
18. Adler AI, Douch E, Dunning L, Elliott N. NICE Guidance on Dapagliflozin for Chronic Heart Failure with Reduced Ejection Fraction. *The Lancet Diabetes & Endocrinology*. 2021;9(5):261-263.

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 Policy Update: RSV Antivirals - Palivizumab

Date of Review: February 2022

Date of Last Review: September 2014
Dates of Literature Search: 06/01/2014 - 10/20/2021

Purpose for Class Update:
To identify new literature since the last update in 2014. Evidence related to the impact of the coronavirus disease 2019 (COVID-19) pandemic on seasonality of respiratory syncytial virus (RSV) onset will be sought, as well as data for the use of palivizumab in children over the age of 24 months who might not have acquired immunity due to lack of exposure to RSV.

Research Questions:
1. Is there any new evidence on the effectiveness of palivizumab on important outcomes such as mortality and hospitalizations due to RSV?
2. Is there any new evidence about harms associated with palivizumab treatment?
3. Are there subpopulations of patients who benefit more from palivizumab prophylaxis?
4. Is there any evidence on the impact of the COVID-19 pandemic on RSV seasonality onset/offset?
5. Is there any evidence to support the use of palivizumab in high-risk children over the age of 24 months?
6. Is there any evidence to support the use of more than 5 doses per RSV season of palivizumab because of differences in seasonality of RSV?

Conclusions:
- New evidence for use of palivizumab for RSV prophylaxis in infants and children does not suggest current Oregon Health Plan (OHP) policy changes are necessary.
- Mitigation measures implemented to curb the spread of COVID-19 virus has led to variances in the typical RSV season. Guidance to address these changes are limited, but the American Academy of Pediatrics (AAP) recommends to monitor interseasonal RSV activity and identify high risk infants who would qualify for palivizumab prophylaxis outside of the traditional RSV season.[1]
- In 2019 AAP reaffirmed their 2014 guidance on use of palivizumab prophylaxis in children, ages 1 month up to 24 months of age, who are at increased risk of hospitalization due to RSV.[2]
- A Cochrane review found no evidence that use of palivizumab for treatment of RSV reduced mortality or length of hospital stay in hospitalized infants and children up to the age of 24 months.[3]
- A second Cochrane review found palivizumab, compared to placebo or no intervention, to reduce hospitalizations due to RSV infections in children at high-risk of RSV infection, based on high quality of evidence (relative risk [RR] 0.44 (95% confidence interval [CI], 0.30 to 0.64).[4] High quality evidence found a reduction in wheezing in children treated with palivizumab compared to placebo or no intervention (RR 0.39; 95% CI, 0.30 to 0.64).[4]
- There is insufficient evidence for the use of palivizumab in high-risk children over the age of 24 months.

Author: Kathy Sentena, PharmD

- There is insufficient evidence for the use of more than 5 doses of palivizumab per RSV season to accommodate for variations in the RSV season.

Recommendations:
- Recommend revising the prior authorization (PA) criteria to correlate with state guidance on season onset.

Summary of Prior Reviews and Current Policy:
- Palivizumab prophylaxis is directed by PA criteria which follows the AAP guidelines for palivizumab use in infants and children that are at high risk of hospitalization from RSV.
- There were 63 pre-covid claims for palivizumab within a 12-month timespan and 38 claims during the 2020-2021 RSV season. Cost per claim for palivizumab prophylaxis represents a substantial cost to Oregon Health Authority (OHA).

Background:
Respiratory syncytial virus is a common cause of lower respiratory infection in infants and children and is the most common cause of bronchiolitis.[5] Approximately 1% to 3% of infections become severe enough to result in hospitalizations and annually there are 59,600 deaths due to RSV worldwide in children under 5 years.[6] Risk factors for the development of severe disease due to RSV include: preterm infants born before 29 weeks gestation, infants with hemodynamically significant congenital heart disease, preterm infants with chronic lung disease, diseases that affect the ability to clear secretions from the upper airway, and immunocompromised children.[7] The AAP published recommendations for the use of palivizumab for prophylaxis of RSV in infants and children at risk of hospitalization in 2014 and reaffirmed these recommendations in a 2019.[2,7]

Palivizumab is a humanized mouse immunoglobulin (IgG1) monoclonal antibody which is indicated for prevention of serious lower respiratory tract disease caused by RSV in children, up to the age of 24 months, at high risk for RSV disease.[7] Data demonstrating reduced RSV hospitalizations with palivizumab immunoprophylaxis comes from two randomized controlled trials.[8,9] The Impact-RSV trial included children born prematurely (≤35 weeks) or with bronchopulmonary dysplasia (BPD).[8] Palivizumab prophylaxis demonstrated reduction in risk of RSV hospitalizations compared to placebo (4.8% vs. 10.6%, respectively).[8] In a second study, the Cardiac Synagis Study Group found that in children with hemodynamically significant CHD, palivizumab prophylaxis reduced RSV hospitalization rates compared to placebo (5.3% vs. 9.7%, respectively).[9] Mortality reduction from RSV due to palivizumab prophylaxis are inconclusive.[7,10,11]

RSV prophylaxis is initiated during high RSV activity. Surveillance data tracks patterns of RSV activity. Generally, the RSV season onset occurs in October or November with an offset in April or May. RSV infection rates were historically monitored via antigen testing. In 2014, the Centers for Disease Control and Prevention (CDC), which provides guidance on RSV testing, incorporated the use of polymerase chain reaction (PCR) laboratory detection.[12] These PCR detections are reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS). The CDC recommends antigen or PCR testing as ways to determine season onset and offset.[13] Season onset occurs when 2 consecutive weeks of mean percentage of specimen testing positive for RSV by antigen tests are at least 10% positive or RSV by PCR tests are at least 3% positive, whichever occurs first.[12,13] In Oregon laboratories report to the OHA/Public Health Division for determination of season onset and offset based on the definition provided by the CDC.

During the COVID-19 pandemic, risk mitigation strategies applied to limit the spread of the COVID-19 virus resulted in variability of the typical seasonal RSV onset, with cases reported in the spring and early summer.[14,2] In June of 2021, the southern region of the U.S. saw an increase in RSV cases prompting the CDC to recommend broader testing.[15] A large RSV resurgence was reported in Tokyo, Japan, with 10,327 cases documented through week 28 of 2021 compared to a

total number of cases in 2020 of 520.[16] Western Australian also reported an unexpected summer RSV surge in late 2020 and hospital admissions occurred in children who were older, median age of 16.4 months compared to 8.1 months in 2019.[17]

The OHA determined the start of the onset of the 2021 RSV season in Oregon was October 2, 2021. RSV rates are reported to the OHA for four regions throughout Oregon and SW Washington and are designated as: northwest Oregon and southwest Washington, central Oregon, the Gorge/northeast Oregon, and southern Oregon. Season onset and offset is determined for the state as a whole, although there is often regional variability in RSV rates.

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 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

Cochrane – Immunoglobulin Treatment for Hospitalized Infants and Young Children with Respiratory Syncytial Virus Infection
A 2019 Cochrane review evaluated the use of immunoglobulins for the treatment of RSV.[3] The anti-RSV immunoglobulin and the monoclonal antibody included in the analysis were palivizumab and motavizumab (not available in the U.S.). Trials included children and infants hospitalized for pneumonia, bronchiolitis, or other lower respiratory tract infection. Seven trials were included in the review, which included children up to 24 months of age (n=486).[3] Only 2 trials evaluated IV palivizumab (1 dose) for the treatment of RSV compared to control (e.g., saline). The main outcomes of interest were mortality, length of hospital stay, and adverse events. Trials were at unclear or high risk of bias for 3 domains and evidence quality was graded as very low to low.

Results were pooled for 5 trials, 2 of which studied palivizumab. For the outcome of mortality there was very low quality evidence that there was no difference between immunoglobulins and control (RR 0.87; 95% CI, 0.14 to 5.27; p=0.88).[3] There was low quality evidence that the length of hospital stay was similar between groups with no benefit demonstrated for immunoglobulins (MD -0.7; 95% CI, -1.83 to 0.42; P=0.66).[3] There was also no statistical difference in adverse event rates or serious adverse event rates.

Overall, there is no evidence that treatment of RSV with palivizumab reduces mortality or length of hospitalization in children 24 months of age or younger.

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[18–22]

Cochrane – Palivizumab for Preventing Severe Respiratory Syncytial Virus (RSV) Infection in Children

A 2021 systematic review and meta-analysis of RCTs evaluated palivizumab use for prevention of RSV in children (maximum 5 doses and ages up to 24 months) compared to placebo or no intervention.[4] Five studies (n=3343) in children at high-risk of RSV infection were included. Participants were infants with a gestational age of 35 weeks or less, diagnosis of bronchopulmonary dysplasia (BPD) or hemodynamically significant congenital heart disease (CHD). All studies evaluated monthly intramuscular (IM) doses of palivizumab 15 mg/kg. Outpatient use of palivizumab was used in all studies and one study also enrolled hospitalized patients. The risk of bias of all five studies was determined by the authors to be low.

A summary of findings with moderate to high quality of evidence are presented in **Table 1**. All outcome results were based on a follow-up period of 2 years. There was low quality evidence that the use of palivizumab resulted in a lower rate of RSV infection compared to placebo or no intervention, 64 per 1000 vs. 195 per 1000.[4]

Table 1. Prevention of RSV Infection in Children Treated with Palivizumab Compared to Placebo or No Intervention[4]

Outcome	Results	Relative Effect	Quality of Evidence
Hospitalizations due to RSV infection	Palivizumab: 43 per 1000 Placebo or no intervention: 98 per 1000	RR 0.44 (95% CI, 0.30 to 0.64)	High
Mortality	Palivizumab: 16 per 1000 Placebo or no intervention: 23 per 1000	RR 0.69 (95% CI, 0.42 to 1.15)	Moderate
Hospitalization due respiratory-related illness	Palivizumab: 274 per 1000 Placebo or no intervention: 341 per 1000	RR 0.78 (95% CI, 0.62 to 0.97)	Moderate
Number of wheezing days	Palivizumab: 18 per 1000 Placebo or no intervention: 45 per 1000	RR 0.39 (95% CI, 0.30 to 0.64)	High
Adverse Events	Palivizumab: 91 per 1000 Placebo or no intervention: 84 per 1000	RR 1.09 (95% CI, 0.85 to 1.39)	Moderate

Palivizumab reduced hospitalizations but mortality benefits at 2 years of follow-up were not demonstrated. The number of respiratory-related illness hospitalizations and number of wheezing days were also reduced with the use of palivizumab.[4]

New Guidelines:
High Quality Guidelines:

American Academy of Pediatrics – Clinical Practice Guideline: The Diagnosis, Management and Prevention of Bronchiolitis
In 2019 the AAP reaffirmed the 2014 guidelines on managing and preventing bronchiolitis in children, ages 1 through 23 months.[5] No data was provided on the reaffirmation process. The AAP guideline was previously presented September 2014 in a Drug Use Research and Management (DURM) RSV Policy Update. A brief review of recommendations for prevention, as it relates to palivizumab, are presented in **Table 2**.[5]

Table 2. Recommendations for the Use of Palivizumab for Prevention of Bronchiolitis[5]

Recommendation	Evidence Quality	Recommendation Strength

Palivizumab should not be administered to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater	B	Strong
Palivizumab should be administered during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants <32 weeks, 0 days' gestation who require >21% oxygen for at least the first 28 days of life	B	Moderate
A maximum of 5 monthly doses (15 mg/kg/dose) of palivizumab should be given in the first year of life to infants who qualify* for palivizumab during the RSV season	B	Moderate
Key: * Detailed guidance on the infants who qualify is described in the AAP guidance on palivizumab prophylaxis which was detailed in the 2014 policy update, including those children up to 24 months of age who would be candidates for prophylaxis		

Additional Guidelines for Clinical Context:

American Academy of Pediatrics – Interim Guidance for Use of Palivizumab Prophylaxis to Prevent Hospitalization from Severe Respiratory Syncytial Virus Infection During the Current Atypical Interseasonal RSV Spread

The traditional RSV season onset and offset was altered due to nonpharmacological measures (i.e., masking, social distancing) used to prevent the spread of COVID-19.[1] The rates of RSV were dramatically lower starting in March of 2020 and activity remained low during the normal fall-winter RSV season of 2020-2021. In the Spring of 2021, there was an interseasonal increase in RSV activity. This increase was thought to be due to relaxation of nonpharmacological measures at around the same time.

Previously published recommendations from AAP for the prophylaxis use of palivizumab for high-risk patients has been used as guidance for identifying the most appropriate candidates for palivizumab use. With evidence of a delayed onset of the 2020-2021 RSV season, AAP supports the use of palivizumab for those patients who have already been identified as appropriate candidates per previous guidance.[1] Early initiation of palivizumab is recommended during the atypical interseasonal variations seen in RSV epidemiology in 2021 for regions that are experiencing high RSV circulation. There was no recommendation for additional doses beyond previous guidance for the use of 5 doses, which continues to provide protection for up to one month after injection. AAP recommends providers assess RSV rates at least monthly and identify eligible infants that may benefit from palivizumab administration.[1]

After review, one guideline was excluded due to poor quality.[23]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 3. 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)
Palivizumab[24]	Synagis	5/2017	Use in specific populations	Palivizumab should not be used in females of reproductive potential

Randomized Controlled Trials:

A total of 123 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

References:

1. American Academy of Pediatrics. Interim Guidance for Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the Current Atypical Interseasonal RSV Spread. Accessed November 2, 2021. Available at: http://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/.

2. AAP Publications Reaffirmed. *Pediatrics*. 2019;144(2):e20191767. doi:10.1542/peds.2019-1767.

3. Sanders SL, Agwan S, Hassan M, et al. Immunoglobulin Treatment for Hospitalised Infants and Young Children with Respiratory Syncytial Virus Infection. *Cochrane Database of Systematic Reviews*. 2019;(8). doi:10.1002/14651858.CD009417.pub2.

4. Garegnani L, Styrmisdóttir L, Rodriguez PR, et al. Palivizumab for Preventing Severe Respiratory Syncytial Virus (RSV) Infection in Children. *Cochrane Database of Systematic Reviews*. 2021;(11). doi:10.1002/14651858.CD013757.pub2.

5. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. *Pediatrics*. 2014;134(5):e1474-1502. doi:10.1542/peds.2014-2742.

6. Haerskjold A, Kristensen K, Kamper-Jørgensen M, et al. Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A Population-based Cohort Study of Danish Children. *Pediatr Infect Dis J*. 2016;35(1):61-65. doi:10.1097/INF.0000000000000924.

7. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants And Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*. 2014;134(2):415-420. doi:10.1542/peds.2014-1665.

8. Impact-RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization from Respiratory Syncytial Virus Infection in High-Risk Infants. Pediatrics. 1998;102:531-537.

9. Feltes T, Cabalka A, Meissner C, et al. Palivizumab Prophylaxis Reduces Hospitalization Due to Respiratory Syncytial Virus in Young Children with Hemodynamically Significant Congenital Heart Disease. J Pediatric. 2003;143:532-40.

10. Andabaka T, Nickerson JW, Rojas-Reyes MX, et al. Monoclonal Antibody for Reducing the Risk of Respiratory Syncytial Virus Infection in Children. *Cochrane Database of Systematic Reviews*. Published online 1996. Accessed July 11, 2013. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD006602.pub4/abstract.

11. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants. *N Engl J Med*. 2013;368(19):1791-1799. doi:10.1056/NEJMoa1211917.

12. Centers for Disease Control and Prevention. Respiratory Syncytial Virus Seasonality - United States, 2014-2017. Morbidity and Mortality Weekly Report. Weekly. January 19, 2018. 67(2);71-76.

13. Oregon Health Authority. RSV-Oregon: Oregon's Weekly Respiratory Syncytial Virus Surveillance Report. Oregon Health Division Acute and Communicable Disease Prevention Program. Week 41. 2021.

14. Barr F, Graham B. Respiratory syncytial virus infection: Prevention in Infants and Children. *UpToDate*. August 2021.

15. Centers for Disease Control and Prevention. Increased Interseasonal Respiratory Syncytial Virus (RSV) Activity in Parts of the Southern United States. Health Alert Network. June 10, 2021.

16. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan - Volume 27, Number 11—November 2021 - *Emerging Infectious Diseases Journal*. doi:10.3201/eid2711.211565.

17. Foley DA, Phuong LK, Peplinski J, et al. Examining the Interseasonal Resurgence of Respiratory Syncytial Virus in Western Australia. *Arch Dis Child*. Published online August 25, 2021:archdischild-2021-322507. doi:10.1136/archdischild-2021-322507.

18. Bloomfield A, DeVincenzo JP, Ambrose CS, Krilov LR. RSV and non-RSV illness Hospitalization in RSV Immunoprophylaxis Recipients: A Systematic Literature Review. *Journal of Clinical Virology*. 2020;1:104339. doi:10.1016/j.jcv.2020.104339.

19. Robinson KA, Odelola OA, Saldanha IJ. Palivizumab for Prophylaxis Against Respiratory Syncytial Virus Infection in Children with Cystic Fibrosis. *Cochrane Database of Systematic Reviews*. 2016;(7). doi:10.1002/14651858.CD007743.pub6.

20. Mauskopf J, Margulis AV, Samuel M, Lohr KN. Respiratory Syncytial Virus Hospitalizations in Healthy Preterm Infants: Systematic Review. *Pediatric Infectious Disease Journal*. 2016;35(7):e229-238. doi:10.1097/INF.0000000000001163.

21. Canadian Agency for Drugs and Technologies in Health. Palivizumab for Infection Prevention in Inuit Infants: A Review of the Clinical Effectiveness and Cost Effectiveness. *Rapid Response*. December 2019.

22. Fauroux B, Simões EAF, Checchia PA, et al. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. *Infect Dis Ther*. 2017;6(2):173-197. doi:10.1007/s40121-017-0151-4.

23. Goldstein M, Philips R, DeVincenzo J, et al. National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration. *Neonatology Today*. 2017;12(10):1-14. doi:10.51362/neonatology.today/20171210114.

24. Synagis (palivizumab) [package insert]. MedImmune, LLC. Gathersburg, MD; May 2017.

Appendix 1: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 18, 2021
Search Strategy:

#	Searches	Results
1	Palivizumab/ or palivizumab.mp.	1184
2	respiratory syncytial virus.mp. or Respiratory Syncytial Viruses/	16722
3	1 or 2	16799
4	limit 3 to (english language and humans and yr="2014 -Current")	4217
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	123

Appendix 2: Key Inclusion Criteria

Population	Infants and children 24 months and younger at high risk of hospitalization
Intervention	Palivizumab prophylaxis
Comparator	No prophylaxis, placebo
Outcomes	Hospitalizations, mortality, recurrent wheeze, asthma
Timing	Prophylaxis during peak RSV activity
Setting	Outpatient or inpatient

Palivizumab (Synagis®)

Goal(s):

- Promote safe and effective use of palivizumab in high-risk infants and children. Prophylaxis against RSV should cover up to 5 months during high viral activity season, usually spanning from November through March in Oregon.

Length of Authorization:

- Based on individual factors; may extend up to 5 months (5 total doses)

Requires PA:

- Synagis (Palivizumab) pharmacy and physician-administered claims

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Has the patient been receiving monthly palivizumab prophylaxis and been hospitalized for a breakthrough RSV infection?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #3
3. Is the request for RSV prophylaxis to be administered during the typical high viral activity season from November through March?	**Yes:** Go to #5	**No:** Go to #4

Approval Criteria		
4. Is the request for prophylaxis starting in October due to interseasonal increase in RSV activity with season onset designated by the OHA*? ~~starting in October due to an early onset* of the RSV season in the region from which the patient resides (see below)?~~ * Data provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated only during high viral activity.
~~4.~~5. Is the current age of the patient < 24 months at start of RSV season?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Not recommended for patients ≥24 months old.
~~5.~~6. **GROUP A** Does the patient have the CLD (chronic lung disease) of prematurity ICD10 Q331through Q339 **and** in the past 6 months has required medical treatment with at least one of the following: a. diuretics b. chronic corticosteroid therapy c. supplemental oxygen therapy	**Yes:** Go to #18	**No:** Go to #7
~~6.~~7. **GROUP B** Has the patient received a cardiac transplant during the RSV season?	**Yes:** Go to #18	**No:** Go to #8

Approval Criteria		
~~7.~~8. **GROUP C** Is the child profoundly immunocompromised during the RSV season (i.e. solid organ transplant or hematopoietic stem cell transplantation)?	**Yes:** Go to #18	**No:** Go to #9
~~8.~~9. **GROUP D** Does the infant have cystic fibrosis and manifestations of severe lung disease or weight or length less than the 10th percentile?	**Yes:** Go to #18	**No:** Go to #10
~~9.~~10. **GROUP E** Is the request for a second season of palivizumab prophylaxis for a child born <32 weeks, 0 days gestation who required at least 28 days of oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of start of second RSV season?	**Yes:** Go to #18	**No:** Go to #11
~~10.~~11. Will the patient be <12 months at start of RSV season?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
~~11.~~12. **GROUP F** Was the infant born before 29 weeks, 0 days gestation?	**Yes:** Go to #18	**No:** Go to #13
~~12.~~13. **GROUP G** Does the infant have pulmonary abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**Yes:** Go to #18	**No:** Go to #14

Approval Criteria		
~~13.~~14. **GROUP H** Does the patient have hemodynamically significant congenital heart disease (CHD) ICD10: P293, Q209, Q220-Q223, Q225, Q229-Q234, Q238, Q240-Q246, Q248-Q249, Q250-Q256, Q278-Q279,Q282-Q283,Q288-Q289, Q2560-Q2565,Q2568-Q2569, Q2570-Q2572, Q2579,Q2731-Q2732 and at least one of the following: a. Acyanotic heart disease who are receiving treatment to control congestive heart failure and will require cardiac surgical procedures; OR b. Have moderate to severe pulmonary hypertension; OR c. History of lesions adequately corrected by surgery AND still requiring medication for congestive heart failure?	**Yes:** Go to #18	**No:** Go to #15
~~14.~~15. **GROUP I** Does the patient have chronic lung disease (CLD) of prematurity defined as gestational age <32 weeks, 0 days and requirement for >21% oxygen for at least the first 28 days after birth?	**Yes:** Go to #18	**No:** Go to #16
~~15.~~16. **GROUP J** Does the patient have cyanotic heart defects and immunoprophylaxis is recommended?	**Yes:** Go to #18	**No:** Go to #17
~~16.~~17. **GROUP K** Does the patient have cystic fibrosis with clinical evidence of CLD and/or nutritional compromise?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~17.~~18. Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	**Yes:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart. May approve for the following on a case-by-case basis: a. >5 doses; b. Prophylaxis for a second / subsequent RSV season	**No:** Go to #19
~~18.~~19. Has the patient had a weight taken within the last 30 days?	**Yes:** Document weight and date and go to #20 Weight:_____ Date:_____	**No:** Pass to RPh. Obtain recent weight so accurate dose can be calculated.
~~19.~~20. Approve palivizumab for a dose of 15 mg/kg. Document number of doses received in hospital and total number approved according to ~~BIRTH DATE and GROUP based on start of RSV season~~month of birth (refer to Table 1): ~~- Immunoprophylaxis between November - March refer to **Table 1**~~ ~~- Immunoprophylaxis starting in October based on above (#4) refer to **Table 2**~~ Total number of doses approved for RSV season:_____ Number of doses received in the hospital:_____ Prior to each refill, the patient's parent/caregiver and prescriber must comply with all case management services, including obtaining current weight for accurate dosing purposes throughout the approved treatment period as required by the Oregon Health Authority.		

Table 1. Maximum Number of Doses for RSV Prophylaxis

~~Beginning **NOVEMBER 1**~~

MONTH OF BIRTH	ALL GROUPS
~~November 1 – March 31~~	~~5~~
April	5
May	5
June	5
July	5
August	5
September	5
October	5
November	5
December	4
January	3
February	2
March	1

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

~~**Table 2**. Maximum Number of Doses for RSV Prophylaxis (based on criteria group from above)~~

~~Beginning **OCTOBER 1**~~

~~MONTH OF BIRTH~~	~~ALL GROUPS~~
~~November 1 – March 31~~	~~5~~
~~April~~	~~5~~
~~May~~	~~5~~
~~June~~	~~5~~
~~July~~	~~5~~
~~August~~	~~5~~
~~September~~	~~5~~
~~October~~	~~5~~
~~November~~	~~5~~
~~December~~	~~4~~
~~January~~	~~3~~
~~February~~	~~2~~
~~March~~	~~1~~

~~* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.~~

Notes:
- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis® is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to 5 doses.
- Approval for more than 5 doses or additional doses after March 31 will be considered on a case-by-case basis. Results from clinical trials indicate that Synagis® trough concentrations greater than 30 days after the 5th dose are well above the protective concentration. Therefore, 5 doses will provide more than 20 weeks of protection.

P&T/DUR Review: *2/22 (KS), 11/16 (DE); 9/14; 5/11; 5/12*
Implementation: *1/1/17; 3/30/12*

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 with New Drug Evaluation: Oral Antifungals

Date of Review: February 2022

Generic Name: ibrexafungerp citrate

Date of Last Review: November 2019
Dates of Literature Search: 08/01/2019 - 11/08/2021
Brand Name (Manufacturer): Brexafemme® (Scynexis, Inc)
Dossier Received: yes

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

Purpose for Class Update:
The purpose of this class update is to review the literature for new comparative evidence since the last class update and evaluate the data for the use of the new antifungal ibrexafungerp.

Research Questions:
1) Is there new comparative evidence related to efficacy for the oral antifungals for important outcomes (e.g., clinical cure or mortality)?
2) Is there new comparative evidence for harms for the oral antifungals?
3) Are there any subpopulations which would receive more benefit or suffer more harm from specific oral antifungals?
4) What is the comparative evidence for efficacy and harms for ibrexafungerp?

Conclusions:
- There was limited new evidence identified since the last antifungal class update in 2019. There was one systematic review and meta-analysis and 2 new randomized controlled trials (RCTs) included in this review.
- A Cochrane review found clinical cure rates to be similar between oral and intra-vaginal antifungals in women with acute, uncomplicated vulvovaginal candidiasis (VVC) based on moderate quality evidence.[1] Moderate quality evidence found short- and long-term mycological cure rates to be higher with oral therapy compared to intra-vaginal therapy.[1]
- The Food and Drug Administration (FDA) approved a new treatment indication and prophylactic indication for posaconazole in 2021. Posaconazole was approved for the treatment of invasive aspergillosis in patients 13 years and older.[2,3] Prophylactic use of posaconazole was broadened to include pediatric patients 2 years and older for prophylaxis against invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients at high risk of developing these infections.[2]
- Secnidazole received an expanded FDA-approved indication for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults in June 2021.[4,5]

Author: Kathy Sentena, PharmD

- There were 2 updated safety warnings for severe cutaneous reactions with voriconazole and risk during pregnancy for isavuconazonium sulfate (**Table 1**).[6,7]
- In June of 2021, ibrexafungerp was approved for treatment of adult and post-menarchal pediatric females with VVC. There is low quality of evidence from two published studies which demonstrated a clinical cure of 50.5% to 63.3% with ibrexafungerp compared to 28.6% to 44% for placebo (number needed to treat [NNT] 5-6).[8, 9]
- There was insufficient evidence for specific subgroup populations to direct oral antifungal therapy.

Recommendations:
- Maintain ibrexafungerp as non-preferred on the preferred drug list (PDL).
- No changes to the PDL are recommended based on review of recently published evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- Presentation of the evidence in the 2019 antifungal class update resulted in no changes to the PDL.
- There is insufficient evidence to strongly support superior efficacy or safety of one oral antifungal over another, with the exception of ketoconazole which is associated with hepatotoxicity, adrenal insufficiency and drug interactions.
- Clotrimazole, fluconazole and nystatin are preferred drugs on the PDL. Griseofulvin, itraconazole, and terbinafine require a prior authorization (PA) due to limited use beyond onychomycosis, which is an unfunded condition.
- Voriconazole and posaconazole are indicated for the treatment of invasive aspergillosis requiring PA approval by a hematologist, oncologist or infectious disease specialist. Approval authorizes use without restriction.
- Oregon Health Plan (OHP) does not fund the treatment of candidiasis of the mouth, skin, nails or dermatophytosis of nail, groin, scalp, and other dematophytosis in immune competent hosts.
- Quarterly expenditures are modest for the antifungal class. Ninety-eight percent of claims are for preferred therapies.

Background:
The antifungal drugs cover a wide spectrum of infections. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies requiring oral or intravenous antifungal therapy.[10] Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality. The FDA recommends that drugs studied for VCC should be evaluated with a primary endpoint of complete absence of all signs and symptoms of VCC.[11] The vulvovaginal signs and symptom (VSS) score is a commonly used tool for determining the severity of VVC. The VSS score is used to access the signs and symptoms of VCC by a standardized, predefined scale, in which a numerical rating is assigned (absent = 0; mild = 1, moderate = 2, severe = 3). Scores are calculated to determine a composite score, ranging from 0-18. Clinical cure is defined as a VSS score of 0 without additional antifungal treatment and clinical improvement is defined as a score of 1 or less.[12]

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines or nucleoside analogs.[13] Choice of antifungal depends on indication, causative organism and resistance patterns. Caspofungin, anidulafungin and micafungin are echinocandins with similar spectrum of action but differing dosing and drug interaction profiles. Echinocandins are most commonly used for serious fungal infections such as invasive candidiasis and as empiric therapy in patients with neutropenic fever.[14] Additionally, echinocandins have been used for salvage therapy in patients with invasive aspergillosis. Amphotericin deoxycholate, liposomal

amphotericin and nystatin are polyene antifungals. Because high risk of nephrotoxicity is associated with systemic formulations of polyenes, these therapies are therefore designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of naftifine and terbinafine. Flucytosine works by a different mechanism of action that allows for use in combination with amphotericin B for severe cryptococcal pneumonia and meningocephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.[15] Drug interactions are common with antifungals and concomitant medications should be considered upon initiation.

Azole antifungals are categorized as either triazoles or imidazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole and ketoconazole). The azole antifungals are effective in treating several types of fungal infections: candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability. Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability in the bioavailability and types of drug interactions (highly metabolized via cytochrome P450 enzyme system) between the different antifungals. Gastrointestinal issues are the most common adverse reactions associated with antifungal therapy and hepatic manifestations from mild elevations to hepatic failure have been demonstrated. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is a recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity. For the initial treatment and salvage therapy triazole antifungals, such as voriconazole and posaconazole, are recommended for the treatment of aspergillosis.[10]

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

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

Systematic Reviews:
Cochrane – Oral versus Intra-vaginal Imidazole and Triazole Antifungal Treatment of Uncomplicated Vulvovaginal Candidiasis (Thrush)
A 2020 Cochrane review evaluated the comparative efficacy of oral versus intra-vaginal triazole anti-fungal treatment for uncomplicated VVC.[1] Twenty-six trials (n=5007 participants) were included in the review. The following antifungals were included (intra-vaginal unless noted): fluconazole (oral), itraconazole (oral), butoconazole, clotrimazole, econazole, miconazole, sertaconazole, and terconazole.[1] Females 16 years and older with a mycological diagnosis (e.g., positive culture or microscopy for yeast) were included. Patients were excluded if they had a history of diabetes, human immunodeficiency virus (HIV), or were currently immunocompromised, pregnant or breast feeding. Main outcomes of interest were mycological cure, adverse reactions, patient preference and symptom relief.

Overall findings suggest no difference in efficacy between oral and intra-vaginal antifungals. Short-term clinical cure (5-15 days) was reported for all trials. Oral versus intra-vaginal treatments were found to have similar efficacy (odd ratio [OR] 1.14; 95% confidence interval [CI], 0.91 to 1.43) based on moderate quality evidence.[1] Long-term clinical cure (2 to 12 weeks) was also found to be similar between treatments (OR 1.07; 95% CI, 0.77 to 1.50; moderate quality evidence).[1]

Moderate quality evidence found short-term mycological cure to be higher with oral antifungals with an estimated incidence of 796 per 1000 patients treated with intra-vaginal treatment compared to 829 per 1000 patients treated with oral antifungals (OR 1.24; 95% CI, 1.03 to 1.50).[1] Long-term mycological cure was also found to be more effective for oral antifungals compared to intra-vaginal antifungals (OR 1.29; 95% CI, 1.05 to 1.60) based on moderate quality evidence. The risk of withdrawing from the trials due to adverse reactions was low in both groups.

All trials were found to be at high risk of blinding of participants, mostly due to route of administration. Most other risk domains were of low risk of bias for a majority of the trials. Evidence on adverse events was considered low quality due to lack of reporting.

After review, 15 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–31]

New Guidelines:
High Quality Guidelines: none identified

Additional Guidelines for Clinical Context: none identified

After review, 2 guidelines were excluded due to poor quality.[16,32]

New Indications:

Posaconazole (Noxafil)® – In June of 2021 posaconazole injection and delayed-release tablets received an indication for the treatment of invasive aspergillosis in patients 13 years of age and older (**Table 2**).[2,3]

Additional expanded indications allow for the prophylactic use of posaconazole delayed-release oral suspension, posaconazole delayed-release tablets and posaconazole injection for broadened age groups. One expanded indication is for those patients 2 years and older, weighing 40 kg or less, who are at high risk of *Aspergillus* and *Candida* infections due to being severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT), those with graft-versus-host disease (GVHD) or those with hematological malignancies with prolonged neutropenia from chemotherapy). Additional expanded indications are for prophylactic use against invasive *Aspergillus* and *Candida* in pediatric patients 2 years or older, weighing 40 kg or more at high risk of developing these infections due to severe immunocompromising disease (e.g., HSCT, those with GVHD or those with hematological malignancies with prolonged neutropenia from chemotherapy, including pediatric populations 2 years and older).[2]

Secnidazole (Solosec®) – In June of 2021 secnidazole was approved for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults.[4] Evidence for approval was based off a multi-center, placebo-controlled, double-blind trial using a single 2-gram oral dose of secnidazole (**Table 2**).[4] Four open-label trials conducted in males and females found a single dose of secnidazole demonstrated efficacy with reported cure rates of 91.7% to 100% at follow up time points of 2 to 20 days.[4] Untreated men had a spontaneous cure rate of 36% (95% CI, 12.8% to 64.9%) at a mean follow-up of 16 days.[4]

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)
Voriconazole[6]	Vfend®	September 2020	Warnings and Precautions	Severe cutaneous reactions (SCARS) (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms) have been reported which can be life threatening or fatal. If SCARS occur then VFEND should be discontinued.
Isavuconazonium sulfate[7]	Cresemba®	May 2021	Warnings and Precautions	Animal reproduction studies demonstrated dose-related increases in multiple skeletal abnormalities in rodents. Isavuconazonium may cause fetal harm and pregnant women should be advised to the potential risk to the fetus.

Randomized Controlled Trials:

A total of 87 citations were manually reviewed from the initial literature search. After further review, 86 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Maertens, et al[3] DB, DD, NI, Phase 3, RCT	Posaconazole IV or oral 300 mg twice on day 1, 300 mg once daily for days 2-84 Vs. Voriconazole 6 mg/kg IV or 300 mg oral twice on day 1 followed by 4 mg/kg IV or 200 mg orally	Patients 13 years and older with proven, probable, or possible invasive aspergillosis N=653	Cumulative all-cause mortality up until day 42 in the ITT population (non-inferiority margin was set at 10%)	Posaconazole: 44 (15%) Voriconazole: 59 (21%) TD -5.3% (95% CI, -11.6 to 1.0) P<0.0001	Posaconazole was non-inferior to voriconazole for all-cause mortality. High attrition in both groups due to death, 32% with posaconazole and 38% with voriconazole. Results most applicable to middle aged, white patients with lower respiratory infection. Analysis of per protocol population is preferred for NI trials. Trial was manufacturer funded.

	twice daily for days 2-84 Treatment was for 12 weeks or less				
Muzny, et al[5] Phase 3, DB, PC, RCT	Secnidazole 2 g orally X 1 dose Vs. Placebo X 1 dose	Females 12 years or older with trichomoniasis (confirmed by positive *T. vaginalis* culture) N=131	Microbiological test of cure (TOC) by culture 6-12 days post dose	Secnidazole: 59 (92.2%) (95% CI, 82.70 to 97.41) Placebo: 1 (1.5%) (95% CI, 0.04 to 8.04) P<0.001 ARR 90.7% / NNT 2	Seconidazole was more effective than placebo for the treatment of trichomoniasis. Results are predominately applicable to women in their thirties who are Black/African American (91% of enrolled patients).

Abbreviations: ARR – absolute risk reduction; DB – double blind; DD – double dummy; ITT – intention to treat; IV – intravenous; NI – non-inferiority; NNT – number needed to treat; PC – placebo controlled; RCT – randomized controlled trial; TD = treatment difference

NEW DRUG EVALUATION:

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:

Ibrexafungerp is a triterpenoid antifungal therapy that disrupts fungal cell formation.[33] Ibrexafungerp is indicated for treatment of adult and post-menarchal pediatric females with VVC. Ibrexafungerp is given orally as a two tablets, totaling 300 mg, twice daily for one day.[33]

Ibrexafungerp was studied in two phase 3 clinical trials to determine efficacy and safety in the treatment of VVC in women (**Table 3**).[33] Women enrolled had a diagnosis of acute VVC with a median baseline composite VSS score of 9.0 in VANISH 303 and 10.0 in VANISH 306 (total score range of 0-18). Both trials compared ibrexafungerp, 300 mg twice daily for one day, to placebo. The primary endpoint was percentage of patients with clinical cure at test-of-cure (TOC), and key secondary endpoints were patients with mycological irradiation and overall success (clinical cure and mycological eradication). TOC was measured at 11 days (±3 days) and symptom assessment (via VSS scale) at day 1 and 25 (±4 days). VSS scores were recorded in a patient diary from day 1 to TOC visit. Rescue therapy was provided to patients with persistent or worsening symptoms and they were considered to early terminators due to lack of efficacy. In VANISH 303, 376 patients were randomly assigned to ibrexafungerp (n=249) or placebo (n=127). Patients were a mean age of 34 years, 54% were white and 41% were Black.[8] Nine percent of study participants were diabetic. In VANISH 306 (n=449) the mean age was 31 years, 81% were Black and 5% were diabetic.[9] In both trials *C. albicans* was the most common species identified, which is consistent with the most common pathogen associated with VVC.[12]

Trial attrition was high in both trials. In VANISH 303 attrition was >20% in both groups due to lack of follow up treatment of cure test.[8] VANISH 306 had attrition rates of 37% for ibrexafungerp and 44% for placebo.[9] Ibrexafungerp demonstrated clinical cure in 50.5% of patients compared to 28.6% of patients taking placebo (relative risk [RR] 1.71; 95% CI, 1.205 to 2.431; p = 0.001; absolute risk reduction [ARR] 21.9%/NNT 5) in VANISH 303. Similar clinical cure rates were

documented in VANISH 306 (66.3% for ibrexafungerp and 44% for placebo; RR 1.38; 95% CI, 1.073 to 1.783; P=0.007; ARR 19.3%/NNT 6).[8,9] The number of patients with mycological irradiation ranged from 49.5% to 58.5% in patients taking ibrexafungerp compared to 19.4% to 29.8% of patients taking placebo. Overall success (clinical cure and mycological eradication) was higher with ibrexafungerp compared to placebo in VANISH 303 (ARR 23.4%/NNT 5) and VANISH 306 (ARR 28.7%/NNT4).[8,9]

Limitations to the evidence include data from two small, single treatment studies to determine treatment efficacy and safety. High dropout rates in both trials resulted in a high degree of attrition bias. Lack of details on outcome assessment could introduce detection bias. The results are most applicable to women with a VSS score around 9-10 who are white, in their thirties and infected with *C. albicans*. There is insufficient evidence for the use of ibrexafungerp in patients with recurrent VVC, in which there are no FDA-approved therapies. Indirect comparisons would suggest similar efficacy to single-dose fluconazole, which is the only other approved oral antifungal for VVC.[9,12]

Clinical Safety:
The most common adverse events experienced in clinical trials at an incidence rate of 2% or more were diarrhea, nausea, abdominal pain, dizziness and vomiting. Ibrexafungerp is contraindicated in pregnancy as it may cause fetal harm, and females of reproductive potential should use effective contraception while taking ibrexafungerp.

Ibexafungerp is metabolized by the CYP3A4 enzyme system and concomitant use with strong CYP3A4 inhibitors increases the concentration and exposure to ibrexafungerp. The dose of ibrexafungerp should be reduced to 150 mg twice daily if given with a strong CYP3A4 inhibitor. Use of ibrexafungerp with strong to moderate CYP3A4 inducers may reduce the exposure and concomitant use should be avoided.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Mycological cure
2) Vulvovaginal signs and symptoms
3) Adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical cure rates

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Ibrexafungerp is a triterpenoid antifungal which inhibits glucan synthase and prevents fungal cell wall formation
Oral Bioavailability	Increased with a high fat meal compared to fasting; not considered clinically significant
Distribution and Protein Binding	Distribution is 600 L 99% protein bound, primarily to albumin
Elimination	Biliary excretion is the primary metabolic pathway
Half-Life	20 hours
Metabolism	Hydroxylation via CYP3A4 followed by glucuronidation and sulfation of a hydroxylated inactive metabolite

Abbreviations: CYP – cytochrome P450 Isoenzymes; L - liters

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. Schwebke, et al[8] (VANISH 303) DB, MC, PC, Phase 3, RCT	1. Ibrexafungerp 300 mg twice daily X 1 day 2. Placebo X 1 day	Demographics: Mean age: 35 years White: 54% Black: 41% Hispanic ethnicity: 24% Diabetic: 9.0% Median composite VSS score: 9.0 Key Inclusion Criteria: - Ages 12 years and older - Diagnosis of acute VVC* - Positive microscopic examination revealing yeast forms and normal vaginal pH (≤4.5) - Use of contraception in patients of reproductive potential Key Exclusion Criteria: - Any condition interfering with diagnosis or evaluation of response - Mixed infections - Systemic or topical vaginal antifungal treatments within 28 days of baseline	ITT: 1. 249 2. 127 mITT: 1. 188 2. 98 Attrition: 1. 61 (24%) 2. 29 (23%)	Primary Endpoint: Percentage of patients with clinical cure† at test-of-cure: Ibrexafungerp: 95 (50.5%) Placebo: 28 (28.6%) RR 1.71 (95% CI, 1.205 to 2.431) P=0.001 Secondary Endpoints: Patients with mycological eradication: Ibrexafungerp: 93 (49.5%) Placebo: 19 (19.4%) RR 2.87 (95% CI, 1.799 to 4.574) P < 0.001 Overall success (clinical cure and mycological eradication): Ibrexafungerp: 64 (36%) Placebo: 12 (12.6%) RR 3.19 (95% CI, 1.772 to 5.756) P < 0.001	ARR 21.9/ NNT 5 ARR 30.1/ NNT 4 ARR 23.4/ NNT 5	Diarrhea: Ibrexafungerp: 55 (22.3%) Placebo: 5 (4.0%) Nausea: Ibrexafungerp: 27 (10.9%) Placebo: 5 (4.0%)	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via an interactive response system. Baseline characteristics were similar between groups except for a higher percentage of black patients in the placebo group and a higher percent of Hispanic/Latino in the ibrexafungerp group. Performance Bias: High. All site and sponsor personnel blinded to treatment assignment. Difference in diarrhea adverse event rates may lead to unblinding of treatment assignment. Members responsible for drug distribution logistics were unblinded. Detection Bias: Unclear. Lab samples assessed via a central lab. No additional details were given on outcome assessment. Attrition Bias: High. Each group had greater than 10% attrition bias. Groups were analyzed via mITT. High attrition was due to lack of positive culture for *Candida* species at baseline. Reporting Bias: Low. Trial protocol was followed. Other Bias: High. Manufacturer funded. **Applicability**: Patient: Results are most applicable to patients infected with the *C. albicans*, which accounted for over 90% of positive cultures. Intervention: Ibrexafungerp dose appropriately determined from a phase 2 study. Comparator: Active treatment comparison would be helpful to determine comparative efficacy. Outcomes: Clinical cure rates and mycological cure are appropriate outcomes to determine efficacy. Setting: 27 study sites in the United States.

		- Pregnant or lactating - HIV infection - Compromised immune system - Cervical/vaginal cancer						
2) Sobel, et al[9] (VANISH 306) DB, MC, PC, Phase 3, RCT	1. Ibrexafungerp 300 mg twice daily X 1 day 2. Placebo X 1 day	Demographics: Mean age: 33 years White: 81% Black: 18% Hispanic ethnicity: 9% Diabetic: 5.0% Median composite VSS score: 10.0 Key Inclusion Criteria: - Same as above Key Exclusion Criteria: - Any condition interfering with diagnosis or evaluation of response - Mixed infections - Systemic or topical vaginal antifungal treatments within 28 days of baseline - Pregnant or lactating - HIV infection - Compromised immune system - Cervical/vaginal cancer	ITT: 1. 298 2. 188 mITT: 1. 151 2. 84 Attrition: 1. 110 (37%) 2. 67 (44%)	Primary Endpoint: Percentage of patients with clinical cure† at test-of-cure: Ibrexafungerp: 119 (63.3%) Placebo: 37 (44.0%) RR 1.38 (95% CI, 1.073 to 1.783) P=0.007 Secondary Endpoints: Patients with mycological eradication: Ibrexafungerp: 110 (58.5%) Placebo: 25 (29.8%) RR 1.85 (95% CI, 1.329 to 2.583) P < 0.001 Overall success (clinical cure and mycological eradication): Ibrexafungerp: 82 (46.1%) Placebo: 23 (28.4%) RR 1.48 (95% CI, 1.038 to 2.113) P = 0.022	ARR 19.3/ NNT 6 ARR 28.7/ NNT 4 ARR 17.7/ NNT 6	Diarrhea: Ibrexafungerp: (6.7%) Placebo: 0 (0%) Nausea: Ibrexafungerp: (7%) Placebo: 0 (0%)	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via an interactive voice or web-based response system. Baseline characteristics were similar between groups except for a higher percentage of Hispanic or Latino patients and patient from Bulgaria in the ibrexafungerp group. Performance Bias: Low. All site and sponsor personnel blinded to treatment assignment. Members responsible for drug distribution logistics were unblinded. Double-dummy design was used to prevent study drug identification. Detection Bias: Unclear. No details were given on outcome assessment. Attrition Bias: High. Each group had greater than 10% attrition bias. A large number of patients (45-48) withdrew before the TOC visit. Groups were analyzed via mITT. Reporting Bias: Low. Trial protocol was followed. Other Bias: High. Manufacturer funded. **Applicability**: Patient: Results are most applicable to white patients infected with the *C. albicans*, which accounted for 89% of positive cultures. Intervention: Ibrexafungerp dose appropriately determined from a phase 2 study. Comparator: Active treatment comparison would be helpful to determine comparative efficacy. Outcomes: Clinical cure rates and mycological cure are appropriate outcomes to determine efficacy. Setting: Nineteen US study sites and 18 sites in Bulgaria

Key: * Defined as a minimum composite vulvovaginal signs and symptoms of 4 or greater with at least 2 signs or symptoms having a score of 2 or more; † VSS score of 0 at test-of-cure visit
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; TOC = test of cure; VSS = vulvovaginal signs and symptoms score; VVC = vulvovaginal candidiasis

References:

1. Denison HJ, Worswick J, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database of Systematic Reviews*. 2020;(8). doi:10.1002/14651858.CD002845.pub3.

2. Noxafil (Posaconazole) [prescribing information]. Whitehouse Sation, NJ; Merck and Co., Inc. June 2021.

3. Maertens JA, Rahav G, Lee DG, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2021;397(10273):499-509. doi:10.1016/S0140-6736(21)00219-1.

4. Solosec (Secnidazole) [prescribing information]. Baltimore, MD. Lupin Pharmaceuticals, Inc. June 2021.

5. Muzny CA, Schwebke JR, Nyirjesy P, et al. Efficacy and Safety of Single Oral Dosing of Secnidazole for Trichomoniasis in Women: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Delayed-Treatment Study. *Clin Infect Dis*. 2021;73(6):e1282-e1289. doi:10.1093/cid/ciab242

6. Food and Drug Administration. Vfend (voriconazole). Drug Safety-related Labeling Changes (SrLC). September 2020.

7. Food and Drug Administration. Cresemba (Isavuconazonium sulfate). Drug Safety-related Labeling Changes (SrLC). May 2021.

8. Schwebke JR, Sobel R, Gersten JK, et al. Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303). *Clin Infect Dis*. Published online September 1, 2021:ciab750. doi:10.1093/cid/ciab750

9. Sobel R, Nyirjesy P,, Ghannoum MA, et al. Efficacy and Safety of Oral Ibrexafungerp for the Treatment of Acute Vulvovaginal Candidiasis: a Global Phase 3, Randomised, Placebo-controlled Superiority Study (VANISH 306). BJOG 2021; https://doi.org/10.1111/1471-0528.16972.

10. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60. doi:10.1093/cid/ciw326.

11. Food and Drug Administration. Vulvovaginal Candidiasis: Developing Drugs for Treatment - Guidance for Industry. Centers for Drug Evaluation and Research. August 2019.

12. Food and Drug Administration. Multi-discipline Review - NDA 214900 Brexafemme (ibrexafungerp). Center for Drug Evaluation and Research. October 12, 2018.

13. Pappas P, Kauffman C, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infec Dis.2016;62:e1-50.

14. Lewis R. Pharmacology of echinocandins. UpToDate. 2019. Accessed August 24, 2019.

15. Drew R, Perfect J. Pharmacology of flucytosine (5-FC). UpToDate. 2019. Accessed August 24, 2019.

16. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. [Review]. *The Lancet Infectious Diseases*. 2019;19(12):e405-e421. doi:10.1016/S1473-3099(19)30312-3

17. Head K, Sharp S, Chong LY, Hopkins C, Philpott C. Topical and systemic antifungal therapy for chronic rhinosinusitis. [Review]. *Cochrane Database of Systematic Reviews*. 2018;1:CD012453. doi:10.1002/14651858.CD012453.pub2.

18. Tenforde MW, Shapiro AE, Rouse B, et al. Treatment for HIV-associated cryptococcal meningitis. *Cochrane Database of Systematic Reviews*. 2018;(7). doi:10.1002/14651858.CD005647.pub3.

19. Murray M, Hine P. Treating progressive disseminated histoplasmosis in people living with HIV. *Cochrane Database of Systematic Reviews*. 2020;(4). doi:10.1002/14651858.CD013594.

20. Shen Loo Y, Yee Wong T, Veettil SK, et al. Antifungal agents in preventing oral candidiasis in clinical oncology: A network meta-analysis. *Oral Diseases*. 2021;27(7):1631-1643. doi:10.1111/odi.13588.

21. Sheng L, Shen Q, Zhou J. Efficacy of different antifungal drugs as initial treatment for patients with talaromycosis: A systematic review and meta-analysis. *Journal de Mycologie Medicale*. 2021;31(1):101108. doi:10.1016/j.mycmed.2020.101108.

22. Sridharan K, Sivaramakrishnan G. Comparative assessment of interventions for treating cutaneous leishmaniasis: A network meta-analysis of randomized clinical trials. *Acta Tropica*. 2021;1:105944. doi:10.1016/j.actatropica.2021.105944.

23. Chen X, Jiang X, Yang M et al. Systematic antifungal therapy for tinea capitis in children. Cochrane Database of Systematic Reviews. 2016. Issue 5. Art. No.: CD004685.

24. Fang J, Huang B, Ding Z. Efficacy of antifungal drugs in the treatment of oral candidiasis: A Bayesian network meta-analysis. [Review]. *Journal of Prosthetic Dentistry*. 2021;125(2):257-265. doi:10.1016/j.prosdent.2019.12.025.

25. Wong TY, Loo YS, Veettil SK, et al. Efficacy and safety of posaconazole for the prevention of invasive fungal infections in immunocompromised patients: a systematic review with meta-analysis and trial sequential analysis. *Scientific Reports*. 2020;10(1):14575. doi:10.1038/s41598-020-71571-0.

26. Gupta AK, Hall S, Zane LT, Lipner SR, Rich P. Evaluation of the efficacy and safety of tavaborole topical solution, 5%, in the treatment of onychomycosis of the toenail in adults: a pooled analysis of an 8-week, post-study follow-up from two randomized phase 3 studies. *Journal of Dermatological Treatment*. 2018;29(1):44-48. doi:10.1080/09546634.2017.1329510.

27. Gupta AK, Bamimore MA, Renaud HJ, Shear NH, Piguet V. A network meta-analysis on the efficacy and safety of monotherapies for tinea capitis, and an assessment of evidence quality. [Review]. *Pediatric Dermatology*. 2020;37(6):1014-1022. doi:10.1111/pde.14353.

28. Yamashita C, Takesue Y, Matsumoto K, et al. Echinocandins versus non-echinocandins for empirical antifungal therapy in patients with hematological disease with febrile neutropenia: A systematic review and meta-analysis. *Journal of Infection & Chemotherapy*. 2020;26(6):596-603. doi:10.1016/j.jiac.2020.01.015.

29. Wang J, Zhou M, Xu JY, Zhou RF, Chen B, Wan Y. Comparison of Antifungal Prophylaxis Drugs in Patients With Hematological Disease or Undergoing Hematopoietic Stem Cell Transplantation: A Systematic Review and Network Meta-analysis. *JAMA Network Open*. 2020;3(10):e2017652. doi:10.1001/jamanetworkopen.2020.17652.

30. Liu W, Feng RZ, Jiang HL. Scedosporium spp lung infection in immunocompetent patients: A systematic review and MOOSE-compliant meta-analysis. *Medicine*. 2019;98(41):e17535. doi:10.1097/MD.0000000000017535.

31. Zhang Z, Zhang X, Zhou YY, Jiang CM, Jiang HY. The safety of oral fluconazole during the first trimester of pregnancy: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2019;126(13):1546-1552. doi:10.1111/1471-0528.15913.

32. Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. *Journal of Clinical Oncology*. 2020;38(27):3205-3216. doi:10.1200/JCO.20.00158.

33. Brexafemme R (ibrexafungerp) [package insert]. Jersey City, NJ, Scynexis, Inc. June 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
clotrimazole	CLOTRIMAZOLE	TROCHE	Y
fluconazole	DIFLUCAN	SUSP RECON	Y
fluconazole	FLUCONAZOLE	SUSP RECON	Y
fluconazole	DIFLUCAN	TABLET	Y
fluconazole	FLUCONAZOLE	TABLET	Y
nystatin	MYCOSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	TABLET	Y
flucytosine	ANCOBON	CAPSULE	N
flucytosine	FLUCYTOSINE	CAPSULE	N
griseofulvin ultramicrosize	GRISEOFULVIN ULTRAMICROSIZE	TABLET	N
griseofulvin, microsize	GRISEOFULVIN	ORAL SUSP	N
griseofulvin, microsize	GRISEOFULVIN	TABLET	N
ibrexafungerp citrate	BREXAFEMME	TABLET	N
isavuconazonium sulfate	CRESEMBA	CAPSULE	N
itraconazole	TOLSURA	CAP SD DSP	N
itraconazole	ITRACONAZOLE	CAPSULE	N
itraconazole	SPORANOX	CAPSULE	N
itraconazole	ITRACONAZOLE	SOLUTION	N
itraconazole	SPORANOX	SOLUTION	N
ketoconazole	KETOCONAZOLE	TABLET	N
posaconazole	NOXAFIL	ORAL SUSP	N
posaconazole	POSACONAZOLE	ORAL SUSP	N
posaconazole	NOXAFIL	TABLET DR	N
posaconazole	POSACONAZOLE	TABLET DR	N
terbinafine HCl	TERBINAFINE HCL	TABLET	N
voriconazole	VFEND	SUSP RECON	N
voriconazole	VORICONAZOLE	SUSP RECON	N
voriconazole	VFEND	TABLET	N
voriconazole	VORICONAZOLE	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303)
Schwebke JR, Sobel R, Gersten JK, Sussman SA, et al. Clinical infectious diseases. 2021; issue 10. [30]

Abstract
BACKGROUND: Current treatment of vulvovaginal candidiasis (VVC) is largely limited to azole therapy. Ibrexafungerp is a first-in-class triterpenoid antifungal with broad-spectrum anti-Candida fungicidal activity. The objective of this study was to evaluate the efficacy and safety of ibrexafungerp compared with placebo in patients with acute VVC. STUDY DESIGN: Patients were randomly assigned 2:1 to receive ibrexafungerp (300 mg twice for 1 day) or placebo. The primary endpoint was the percentage of patients with a clinical cure (complete resolution of vulvovaginal signs and symptoms [VSS]=0) at test-of-cure (day 11). Secondary endpoints included the percentage of patients with mycological eradication, overall success (clinical cure and mycological eradication), clinical improvement (VSS?1) at test-of-cure, and symptom resolution at follow-up (day 25). RESULTS: Patients receiving ibrexafungerp had significantly higher rates of clinical cure (50.5% [95/188] vs 28.6% [28/98]; P=0.001), mycological eradication (49.5% [93/188] vs 19.4% [19/98]; P<0.001), and overall success (36.0% [64/178] vs 12.6% [12/95]; P<0.001) compared with placebo. Symptom resolution was sustained and further increased with ibrexafungerp compared with placebo (59.6% [112/188] vs 44.9% [44/98]; P=0.009) at follow-up. Post hoc analysis showed similar rates of clinical cure and clinical improvement at test-of-cure for African American patients (54.8% [40/73] and 63.4% [47/73], respectively) and patients with a body mass index >35 (54.5% [24/44] and 68.2% [30/44], respectively) compared with overall rates. Ibrexafungerp was well tolerated. Adverse events were primarily gastrointestinal and mild in severity.
CONCLUSION: Ibrexafungerp provides a promising safe and efficacious oral treatment that mechanistically differs from current azole treatment options for acute VVC.

Efficacy and Safety of Single Oral Dosing of Secnidazole for Trichomoniasis in Women: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Delayed-Treatment Study
Christina A Muzny, Jane R Schwebke, Paul Nyirjesy, et al.

Background: Trichomonas vaginalis is the most prevalent nonviral sexually transmitted infection. We evaluated the efficacy and safety of secnidazole vs placebo in women with trichomoniasis.
Methods: Women with trichomoniasis, confirmed by a positive T. vaginalis culture, were randomized to single-dose oral secnidazole 2 g or placebo. The primary endpoint was microbiological test of cure (TOC) by culture 6-12 days after dosing. At the TOC visit, participants were given the opposite treatment. They were followed for resolution of infection afterward and offered treatment at subsequent visits, if needed. Fifty patients per group (N = 100) provided approximately 95% power to detect a statistically significant difference between treatment groups.
Results: Between April 2019 and March 2020, 147 women enrolled at 10 sites in the United States. The modified intention-to-treat (mITT) population included 131 randomized patients (secnidazole, n = 64; placebo, n = 67). Cure rates were significantly higher in the secnidazole vs placebo group for the mITT population (92.2% [95% confidence interval {CI}: 82.7%-97.4%] vs 1.5% [95% CI: .0%-8.0%]) and for the per-protocol population (94.9% [95% CI: 85.9%-98.9%] vs 1.7% [95% CI: .0%-8.9%]). Cure rates were 100% (4/4) in women with human immunodeficiency virus (HIV) and 95.2% (20/21) in women with bacterial vaginosis (BV). Secnidazole was generally well tolerated. The most frequently reported treatment-emergent adverse events (TEAEs) were vulvovaginal candidiasis and nausea (each 2.7%). No serious TEAEs were observed.
Conclusions: A single oral 2 g dose of secnidazole was associated with significantly higher microbiological cure rates vs placebo, supporting a role for secnidazole in treating women with trichomoniasis, including those with HIV and/or BV.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 08, 2021
Search Strategy:

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	3111
2	fluconazole.mp. or Fluconazole/	14874
3	nystatin.mp. or Nystatin/	5323
4	flucytosine.mp. or Flucytosine/	3824
5	griseofulvin.mp. or Griseofulvin/	3961
6	ibrexafungerp.mp.	64
7	isavuconazonium.mp.	70
8	Itraconazole/ or itraconazole.mp.	10895
9	ketoconazole.mp. or Ketoconazole/	9485
10	posaconazole.mp.	3043
11	terbinafine.mp. or Terbinafine/	3161
12	voriconazole.mp. or Voriconazole/	7547
13	vaginal candidiasis.mp.	964
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 12	48959
15	limit 14 to (english language and humans and yr="2019 -Current")	2808
16	limit 15 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	87

Appendix 4: Prescribing Information Highlights

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

BREXAFEMME® (ibrexafungerp tablets), for oral use
Initial US Approval: 2021

----------INDICATIONS AND USAGE----------
BREXAFEMME is a triterpenoid antifungal indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg. (2.1)
- BREXAFEMME may be taken with or without food. (2.1)
- Prior to initiating treatment, verify pregnancy status in females of reproductive potential. (2.3)

----------DOSAGE FORMS AND STRENGTHS---------
Tablets: 150 mg of ibrexafungerp (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Hypersensitivity to ibrexafungerp. (4)

----------WARNINGS AND PRECAUTIONS----------
Risk of Fetal Toxicity: May cause fetal harm based on animal studies. Advise females of reproductive potential to use effective contraception during treatment. (2.3, 5.1, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most frequent adverse reactions (≥ 2%) reported with BREXAFEMME in clinical trials of vulvovaginal candidiasis treatment were diarrhea, nausea, abdominal pain, dizziness, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SCYNEXIS, Inc. at 1-888-982-7299 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Concomitant use of strong CYP3A inhibitors increases the exposure of ibrexafungerp. Reduce BREXAFEMME dose with concomitant use of a strong CYP3A inhibitor to 150 mg twice daily for one day. (2.2, 7)
- Concomitant use of strong and moderate CYP3A inducers may significantly reduce the exposure of ibrexafungerp. Avoid concomitant administration of BREXAFEMME with strong or moderate CYP3A inducers. (7)

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

Revised: 6/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for antifungal therapy
Intervention	Oral antifungal
Comparator	Other antifungals or placebo
Outcomes	Mortality, clinical cure, mycological cure, symptom resolution
Timing	Onset of infection
Setting	Outpatient or inpatient

Antifungals

Goal(s):

- Approve use of antifungals only for OHP-funded diagnoses. Minor fungal infections of skin, such as dermatophytosis and candidiasis are only funded when complicated by an immunocompromised host.

Length of Authorization:

- See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Table 1: Examples of FUNDED indications (12/16/21~~1/1/15~~)

ICD-10	Description
B37.3	Candidiasis of vulva and vagina
B37.1	Candidiasis of the lung
B37.7	Disseminated Candidiasis
B37.5-37.6, B37.81-37.8~~42~~, B37.8~~94~~-37.90~~89~~	Candidiasis of other specified sites
B38.0-B38.4, B38.7~~89~~, B38.9	Coccidiomycosis various sites
B39.0~~2~~-39.5, B39.9, G02, I32, I39, J17	Histoplasmosis
B40.9,B41.0, B41.9, B48.0	Blastomycosis
B42.0-42.9~~7~~, ~~B429~~, B43.9, B44.9-45.0, B45.7, B45.9, B46.9, B48.1-48.2, B48.8, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycosis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
B48.8	Mycosis, Opportunistic
B44.81	Bronchopulmonary Aspergillus, Allergic

N73.9-75.1, N75.9, N76.0-N77.1(~~except N72)~~	Inflammatory disease of cervix vagina and vulva
L03.019,L03.029, L03.039, L03.049	Cellulitis and abscess of finger and toe
P37.5	Neonatal Candida infection
B37.42,B37.49	Candidiasis of other urogenital sites

Table 2: Examples of NON-FUNDED indications (12/16/21~~1/1/15~~)

ICD-10	Description
L2.083, L2.10-2.11, L21.8-21.9, ~~L303~~	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L20.0-20.8~~42~~, L20.8~~94~~-20.~~989~~	Other atopic dermatitis and related conditions
L24.0-24.2, L25.1-25.5, L57.8, L57.9, L23.0, L23.81, L24.81, L25.0, L25.2, L25.8-25.9, L55.1-55.2 , L56.8, L58.9	Contact dermatitis and other eczema
L53.0-53.2, L51.0, L51.8-51.9, L52, L71.0-71.1, L71.8, L93.0, L93.2, L49.0-L49.9, L26, L30.4, L53.8, L92.0, L95.1, L98.2, L53.9	Erythematous conditions
L43.8,L44.1-44.3, L44.9,L66.1	Lichen Planus
L70.0-70.2, L70.8	Rosacea or acne
B35.1	Tinea unguium (onychomycosis)
B36.0	Pityriasis versicolor
B36.2	Tinea blanca
B36.3	Black piedra
B36.8, B36.9	Mycoses, superficial
B37.2	Cutaneous candidiasis
B37.9	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

Table 3: Criteria driven diagnoses (12/16/21~~1/1/15~~)

ICD-10	Description
B35.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)

B35.2	Dermatophytosis of hand (tinea manuum)
B35.6	Dermatophytosis of groin and perianal area (tinea cruris)
B353	Dermatophytosis of foot (tinea pedis)
B35.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
B35.8	Deep seated dermatophytosis
B35.8-B35.9	Dermatophytosis of other specified sites - unspecified site
B36.1	Tinea nigra
~~B370~~,B37.83	Candidiasis of mouth
~~B3742,B3749~~	~~Candidiasis of other urogenital sites~~

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	**Yes:** Go to #3	**No:** Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Approve for 3 months or course of treatment.
4. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole or posaconazole?	**Yes:** Approve for 3 months or course of treatment.	**No:** Go to #5
5. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** Pass to RPh. Deny; not funded by OHP	**No:** Got to #6
6. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #7	**No:** Go to #9

Approval Criteria		
7. Is the patient immunocompromised (examples below)? • Does the patient have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR** • Does the patient have a diagnosis of HIV/AIDS? **OR** • Does the patient have sickle cell anemia? • Poor nutrition, elderly or chronically ill? • Other conditions as determined and documented by a RPh.	**Yes:** Record ICD-10 code. Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #8

Approval Criteria		
8. Is the patient currently taking an immunosuppressive drug? Document drug. **Pass to RPh for evaluation if drug not in list.** Immunosuppressive drugs include but are not limited to: azathioprine, basiliximab, cyclophosphamide, cyclosporine, etanercept, everolimus, hydroxychloroquine, infliximab, leflunomide, mercaptopurine, methotrexate, mycophenolate, rituximab, sirolimus, tacrolimus	**Yes:** Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Pass to RPh. Deny; not funded by the OHP

9. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis:
 	
• If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.
• If not funded: Deny; not funded by the OHP.
  ○ Deny non-fungal diagnosis (medical appropriateness)
  ○ Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).
  ○ Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.		

P&T Review: *2/22 (KS); 11/19 (KS); 7/15; 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*

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 with New Drug Evaluation: Drugs for Pompe Disease

Date of Review: February 2022

Date of Last Review: April 2021
Dates of Literature Search: 4/1/2021- 11/05/2021
Generic Name: avalglucosidase alfa-ngpt
Brand Name (Manufacturer): Nexviazyme™ (Genzyme Corporation)
Dossier Received: yes

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

Purpose for Class Update:
The purpose of the Pompe Disease drug class update is to evaluate new literature published since the last review and to evaluate the efficacy and safety of avalglucosidase alfa, a new formulation of recombinant human acid alfa glucosidase (GAA).

Research Questions:
1. What is the efficacy and effectiveness of alglucosidase alfa or avalglucosidase alfa in reducing symptoms, improving functional outcomes, and improving mortality in patients with Pompe disease?
2. What are the harms of alglucosidase alfa or avalglucosidase alfa 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 or avalglucosidase alfa therapy?

Conclusions:
- The safety and efficacy of avalglucosidase alfa was assessed in one phase 3, randomized, double-blind multinational, multicenter non-inferiority (NI) trial in enzyme replacement therapy (ERT)-naïve late-onset Pompe disease (LOPD) patients aged 16 years and older.[1,2] In the 49-week study, patients (n=100) were randomly allocated in a 1:1 ratio to either avalglucosidase alfa 20 mg/kg (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49).[1,2] The study is unpublished so risk of bias could not be fully assessed.
- The primary outcome was least square means (LSM) change in percent of predicted forced vital capacity (FVC) in the upright position from baseline to 49 weeks.[1,2] The NI margin for the lower bound of the two-sided 95% confidence interval (CI) for the difference between the two treatment arms was set at -1.1%.[1] At 49 weeks, the estimated mean change from baseline in percent predicted FVC was higher in the avalglucosidase alfa arm (2.9%) versus alglucosidase alfa (0.5%) with an estimated treatment difference of 2.4% (95% CI -0.1 to 5.0; p=0.06) in favor of avalglucosidase alfa.[1,2] The trial met noninferiority for the primary efficacy endpoint but did not achieve statistical superiority.[1]

Author: David Engen, PharmD

- Clinically relevant secondary endpoints evaluated the estimated treatment difference of distance walked in the 6-minute walk test (6MWT) and health-related quality of life as measured by the 12-item short form health survey (SF-12).[1,2] The estimated mean change from baseline to week 49 in the 6MWT was higher in the avalglucosidase alfa arm (32.2 meters) versus avalglucosidase alfa (2.2 meters) with an estimated treatment difference of 30.0 meters (95% CI 1.3 to 58.7; p=0.04) in favor of avalglucosidase alfa.[1,2] There were no statistically significant differences between groups in the SF-12 score at week 49 compared to baseline.[1]
- The most common adverse events that occurred during treatment over 49 weeks in the avalglucosidase and alglucosidase groups, respectively, were headache (22% vs. 33%), fatigue (18% vs. 14%), diarrhea (12% vs. 16%), nausea (12% vs. 14%), arthralgia (10% vs. 16%), dizziness (10% vs. 8%), and myalgia (10% vs. 14%).[1,2]
- FDA labeling has a black boxed warning (BBW) for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs) and risk of acute cardiorespiratory failure in susceptible patients.[2] More frequent monitoring of vital signs should be performed during infusion for susceptible patients.[2] If severe IAR occurs, therapy should be immediately discontinued and appropriate medical treatment initiated.[2] Those with higher risk for IARs include patients with:
  - -advanced Pompe disease
  - -susceptibility to fluid volume overload
  - -acute underlying respiratory illness
  - -compromised cardiac or respiratory function necessitating fluid restriction.[2]
- There is low-quality evidence of no difference between alglucosidase alfa 20 mg/kg and 40 mg/kg in safety and effectiveness for the treatment of IOPD based on one systematic review.[3]
- There is insufficient evidence to evaluate the use of avalglucosidase alfa in the treatment of specific subpopulations based on age, gender, race, ethnicity, comorbidities, disease duration or severity.

Recommendations:
- Add avalglucosidase alfa to the Lysosomal Storage Disorders preferred drug list (PDL) class and designate as non-preferred.
- Update prior authorization criteria for Pompe Disease drugs and incorporate avalglucosidase alfa clinical criteria to ensure appropriate use.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Pharmacotherapy for Pompe disease was last reviewed by the Pharmacy and Therapeutics (P & T) meeting in April of 2021. At that time, alglucosidase alfa was added to the Lysosomal Storage Disorders PDL class and remained non-preferred. Prior authorization (PA) criteria was implemented for alglucosidase alfa to ensure medically appropriate use. Additional PA revisions were approved by the P & T Committee to ensure safe and appropriate utilization of alglucosidase alfa, including the recommendation that newly started patients be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.

Background:

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a rare inherited, degenerative disease caused by pathogenic alpha-glucosidase gene variants which result in a deficiency of the lysosomal alpha glucosidase (GAA).[4,5] GAA mutations lead to a nonfunctional GAA enzyme and lysosomal accumulation of glycogen stored in skeletal and cardiac muscle as well as other tissues. [4,5] 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. [4,5] Generally, early deficiencies in GAA activity result in rapid progression of disease and decline of motor function.[4,5] Although Pompe disease typically presents within the first 2 months of life, it can also manifest beyond infancy. [4,5] Early-onset Pompe disease with symptoms of cardiomyopathy, if left untreated, typically results in death from cardiorespiratory failure by the second year of life. [4,5]

It is estimated that Pompe disease affects roughly 1:40,000 people worldwide. In the United States, prevalence of Pompe is estimated between 1 in 21,979 and 1 in 9,625 births, while African Americans may represent a rate as high as 1:14,000.[6,7,8] Risk factors for development of Pompe disease include family history of glycogen storage disease (Type 2) where, at conception, siblings of a patient have a 25% chance of disease development.[8] A claims-based review from 1/1/2020-12/31/2020 revealed 15 patients in the Oregon Health Plan (OHP) population with a Pompe disease diagnosis, 3 of whom were Fee-for-Service (FFS) members. Pompe disease is a funded condition on line 147 (glycogenosis) of the Health Evidence Review Commission (HERC) prioritized list of health services. In Oregon, newborn screening (NBS) for Pompe disease is available through the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Program.[9]

Clinical presentation of Pompe disease differs based on the age of onset, type of organs involved, progression rate, and severity.[10,11] Infantile-onset Pompe Disease (IOPD) generally presents before 12 months of age (median age ~4 months), with rapid progression of symptoms such as muscle weakness, respiratory distress, and cardiac complications.[10] The hallmark of IOPD is cardiomyopathy although the mechanism is poorly understood. Most IOPD patients die of cardiac and respiratory failure without achievement of motor milestones such as turning over, sitting, or crawling. [10,11] Late-onset Pompe disease (LOPD) describes individuals who generally present after 12 months and without cardiac involvement.[10,11] 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.[10,11] Osteoporosis, scoliosis, small-fiber neuropathy, sleep apnea, hearing loss, dysphagia, impaired gastric function, fatigue, and risk of cerebral aneurisms and cardiac arrhythmia are also common in LOPD patients.[12] Respiratory dysfunction from intercostal and accessory muscle decline commonly leads to mortality through respiratory failure. [4,5] Male gender and an earlier age of onset may predict a more rapid disease course in LOPD patients.[10,11] 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. [10,11] However, with LOPD able to manifest at any age after infancy, a classification scheme based on age is difficult.[11] **Table 1** highlights some general features which distinguish IOPD from LOPD.

Table 1: General Characteristics of IOPD versus LOPD[10,11]

IOPD	**LOPD**
Onset <u>≤</u>12 months old **with** cardiomyopathy	Onset <12 months **without** cardiomyopathy <u>or</u> Onset >12 months into adulthood
Typical age at diagnosis: <1-year-old	Typical age at diagnosis: roughly 40 years old
Alfa glucosidase enzyme activity <1% normal (Complete deficiency)	Alfa glucosidase 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 GAA gene is located on chromosome 17q25 and hundreds of variations have been identified.[8,13] 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.[8,13] The clinical course of disease depends upon the type of mutation and subsequent residual GAA activity.[14] Numerous mutations have been found common to patients of certain ethnicities. Many Taiwanese patients with Pompe disease share mutations in p.Asp645Glu.[15] In African-American patients, the p.Arg854Ter mutation can be traced back to populations of North Central Africa.[16] One study traced two separate cases of early Pompe disease to a small region in Mexico where the individuals shared the same c.1987delC frameshift mutation.[17] The GAA mutation most frequently found among Caucasian children and adults with Pompe disease is c.-32-13T>G.[18] However, there are at least two known variants (c.1726G>A and c.2065G>A) that cause a pseudodeficiency where low levels of GAA activity are found with no evidence of clinical disease.[19,20] This pseudodeficiency has been noted at a high frequency in the Asian population which may increase false-positive newborn screening results.[19,20] Typically, 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.[10,11] 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.[10,11]

Treatment for Pompe disease may include a variety of strategies which depend upon patient age, stage, genetic factors, and clinical manifestations.[10,11,13,21] Management usually requires a multidisciplinary approach with expertise in cardiology, pulmonology, metabolic disease, neurology, rehabilitation services, and nutrition support.[10,11,13] Respiratory, motor, and nutritional assessments are needed at regular intervals to track disease activity and monitor progress.[10,11,13] Some studies suggest that enhanced nutrition and exercise may help slow muscle function decline in LOPD patients.[10,11,13] A cardiology evaluation with chest X-rays and echocardiography may be of value to monitor left ventricular mass index (LMVI) and risk of sudden cardiac death.[10,11,13,22] Respiratory surveillance is accomplished through regular pulmonary function tests (PFTs) to ensure airway integrity.[10,11,13] For those patients with a need for respiratory support, supplemental oxygen or non-invasive ventilatory support may be warranted.[10,11,13] Assessment of musculoskeletal changes and function via magnetic resonance imaging (MRI), periodic scoliosis tests, and bone mineral density scans are also suggested.[10,11,13] 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.[10,11,13]

Enzyme replacement therapy (ERT) has been studied for many clinical outcomes in Pompe disease including mortality, respiratory function, ventilator dependence, and walking distance, but its effectiveness for all types and stages of disease has shown mixed results.[23] In IOPD, ERT is typically started upon diagnosis or once symptomatic Pompe disease is recognized.[10,11,13] The benefit of ERT in LOPD patients is less clear and may be dependent upon clinical signs, symptoms and rate of progression.[10,11,13] Although ERT has been a major breakthrough in prolonging survival, it is not a cure and it has significant limitations such as the potential for severe infusion-related reactions and/or extremely high antibody titers with negative effects on treatment efficacy.[23]

Almost all Pompe patients develop antibodies to exogenous ERT, but the response is especially problematic in those IOPD patients with no endogenous GAA. IOPD patients with two GAA mutations and unable to synthesize the GAA enzyme are categorized as cross-reactive immunological material (CRIM)-negative.[24] LOPD patients and GAA-deficient IOPD patients with at least some residual functional enzyme are known as CRIM-positive patients.[24] 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.[24] Some studies have shown that CRIM-negative patients experienced more clinical decline, required invasive ventilation, and had increased risk of death regardless of ongoing ERT.[24] Severe immune responses during ERT have included hypersensitivity reactions, hypercoagulation, and anaphylaxis.[25-27] CRIM status is determined by Western blot analysis of patient fibroblast cells.[24] Prior to ERT, the patient's CRIM status is ascertained to assess the need for concomitant immune tolerance induction (ITI) therapy to optimize response to ERT and avoid the potential for immune-mediated reactions and poor outcomes.[10,11,13,28] Various protocols have been developed for tolerance induction in CRIM-negative patients. 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.[29] Considerations for starting and stopping ERT based upon European consensus are listed in **Table 2**.

Table 2: Considerations for Starting and Stopping Enzyme Replacement Therapy[29]

Starting Enzyme Replacement Therapy (ERT)	Stopping Enzyme Replacement Therapy (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. Pulmonary function assessment in Pompe disease patients is often obtained by measurement of FVC and maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively).[27] Diaphragm weakness is suspected if there is a 10% or greater decrease of FVC in the supine compared with the upright position; a 30% or greater decrease indicates severe weakness.[30] In chronic diseases such as chronic obstructive pulmonary disease (COPD), at least a 15% change over a year has been considered clinically meaningful.[31] The six-minute walk test (6MWT) has been used to measure gross motor function and the functional exercise level for daily physical activities in Pompe disease patients.[25,27] Normal values for the 6MWT in healthy adults are at least 500 meters but can be as high as 700 meters in healthy adolescents.[25,27] The 6MWT has been extensively used to measure response to treatment in patients with chronic disease such as COPD and heart failure.[31] 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.[31] The Pompe Pediatric Evaluation of Disability Index (Pompe-PEDI) is used in children from roughly 6 months to 14 years old and measures mobility, function, and self-care in Pompe disease. [25,27] 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.[25,27] The higher the score, the more skills the child can perform.[25,27] The 36-item Short-Form Health Survey (SF-36) is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[32] 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. The 12-item Short Form Health Survey (SF-12) is an abbreviated version of the SF-36 which is comprised of a physical component summary (PCS) and mental health component summary (MHC) scale score.[33] The SF-12 uses the same 8 domains found in the SF-36 but only includes one or two items from each of the eight SF-36 scale sections.[33] As with the SF-36, the SF-12 score ranges from 0-100 (high score indicates better physical function).[33] Both the SF-12 and SF-36 have been found to correlate closely with one another.[33] Although the 6MWT, FVC, Pompe PEDI, SF-36, and SF-12 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.[34]

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

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

Systematic Reviews:
A 2017 Cochrane systematic review assessed the safety, effectiveness, and appropriate dose regimen of enzyme replacement therapy for the treatment of IOPD.[3] Only a single low-quality trial (N=18) was identified which evaluated hospitalized infants (<26 weeks of age at enrollment) with confirmed IOPD.[3] The study compared two different alglucosidase alfa dose regimens (20 mg/kg versus 40 mg/kg) given at 2-week intervals.[3] The alglucosidase alfa treatment results were also compared to an untreated historical control group.[3] Overall, there was low-quality evidence of no difference between the 20 mg/kg and 40 mg/kg treatment groups for outcomes in cardiac function, motor development, and proportion of children free of invasive ventilation at 52 weeks.[3] Quality of evidence was limited due to lack of blinding, unclear random sequence generation and allocation concealment, and poor reporting of study methods as there were little to no numerical results available by dose group.[3] The trial also reported that long-term alglucosidase alfa treatment extended survival as well as ventilation-free survival and improved cardiomyopathy compared to the untreated control group, but the magnitude of benefit could not be quantitatively analyzed, and the quality of evidence was downgraded due to selective reporting.[3] A meta-analysis showed no significant difference for infusion-related events between the high and low-dose alglucosidase alfa treatment groups.[3]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No high-quality guidelines were identified which met quality inclusion criteria.

Additional Guidelines for Clinical Context:
A multidisciplinary panel of Canadian physicians released consensus guidelines for healthcare professionals who are involved in the care of patients with Pompe disease.[35] Although it was reported that the level of evidence was examined and graded based on the Oxford Centre for Evidence-Based Medicine and the international GRADE group approach to clinical guidelines, no methodological details were reported.[35] There was no systematic guideline development method described, strength of evidence for guideline recommendations were not provided, and the recommendations were based on expert opinion.[35] In addition, the authors reported several conflicts of interests including providing consultative services to the manufacturer Genzyme as well as receiving research support and consultancy fees.[35] Based these factors, the recommendations from this publication were excluded from this review.

New Formulations or Indications:
None

New FDA Safety Alerts:
None

Randomized Controlled Trials:
A total of 28 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

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:
Avalglucosidase alfa (Nexviazyme™) is a recombinant human acid alfa glucosidase approved for use in patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency).[1,2] Avalglucosidase is a prodrug of the previously marketed alglucosidase alfa (Lumizyme™) and is administered as an intravenous infusion at a dose of either 20 mg/kg (patients ≥30 kg) or 40 mg/kg (patients <30 kg) once every 2 weeks.[1,2] The FDA approved avalglucosidase alfa in 2021 for the treatment of patients 1 year of age and older with late-onset Pompe disease.[1,2]

Safety and efficacy of avalglucosidase alfa was assessed in one unpublished, phase 3, randomized, double-blind, multinational, multicenter NI trial in ERT-naïve LOPD patients aged 16 years and older (EFC14028 "COMET"- **Table 5**).[1,2] Patients (n=100) were randomly allocated in a 1:1 ratio to either avalglucosidase alfa 20 mg/kg (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49) for 49 weeks.[1,2] There were differences is a number of baseline characteristics. The avalglucosidase alfa arm had fewer Hispanic or Latino representation, while the alglucosidase alfa arm contained no patients of Asian descent.[1] Baseline mean and median percent predicted FVC and distance walked in the 6MWT were higher in the avalglucosidase alfa arm than in the alglucosidase alfa arm.[1] In addition, there were slightly more patients in the avalglucosidase arm that did not require walking device assistance.[1] Patient ages ranged from 16 to 78 years and the mean and median ages for the two arms was roughly 48 years.[1] Mean disease duration for both arms was about 13 years, but the range was wider in the avalglucosidase arm (0.9 to 58.2 years) compared to alglucosidase (0.4 to 38.2 years).[1] Patients were excluded if they had any prior alglucosidase or ITI therapy, were dependent upon invasive ventilation, were unable to perform repeated percent predicted FVC measurements in upright position of between 30% and 85%, were unable to ambulate 40 meters without stopping and without an assistive device, or had known history of Pompe-specific cardiac hypertrophy.[1] The primary outcome was LSM change in percent predicted FVC in the upright position from baseline to 49 weeks.[1,2] The non-inferiority (NI) margin for the lower bound of the two-sided 95% confidence interval for the difference between the two treatment arms was set at -1.1%.[1] The NI margin of -1.1% was determined using the results of trial AGLU02704 (LOTS), a phase 3, randomized, double-blinded, placebo-controlled, superiority trial of alglucosidase alfa.[1] Clinically relevant secondary endpoints were the estimated treatment difference of distance walked in the 6MWT and health-related quality of life as measured by the SF-12.[1] The

49-week study was followed by an open-label treatment period of up to 144 weeks in which all participants received avalglucosidase alfa regardless of their original randomization group.[1]

Ninety-five of the enrolled 100 patients completed the trial.[1] At 49 weeks, the estimated mean change from baseline in percent predicted FVC was higher in the avalglucosidase alfa arm (2.9%) versus alglucosidase alfa (0.5%) with an estimated treatment difference of 2.4% (95% CI -0.1 to 5.0; p=0.06) in favor of avalglucosidase alfa.[1,2] With the lower bound of the 95% CI for the difference larger than the prespecified NI margin (-1.1%), the trial met noninferiority for the primary efficacy endpoint but did not achieve statistical superiority.[1] The estimated mean change from baseline to week 49 in the 6MWT was higher in the avalglucosidase alfa arm (32.2 meters) versus alglucosidase alfa (2.2 meters) with an estimated treatment difference of 30.0 meters (95% CI 1.3 to 58.7; p=0.04) in favor of avalglucosidase alfa.[1] For the other secondary endpoints including SF-12 PCS and SF-12 MCS scores, there were no statistically significant differences between groups compared to baseline.[1]

The FDA reviewed data from the open-label extension trial where all remaining patients who had received alglucosidase alfa treatment were switched over to avalglucosidase alfa 20 mg/kg to continue treatment every other week until week 97.[1] There were 23/44 patients available for assessment of the primary outcome at the data cutoff point.[1] The mean change in percent predicted FVC from week 49 to week 97 among the 23 patients was -0.1% (95% CI -3.2 to 2.8; p=0.92), which failed to show a statistically significant improvement.[1] There were 26/44 crossover patients available for assessment of the 6MWT during the same time period and the mean change in distance walked in 6MWT from week 49 to 97 among the 26 patients was 8.6 meters (95% CI -20.4 to 37.5; p=0.55), which also failed to show a statistically significant improvement.[1]

A third unpublished, phase 2, open-label, ascending dose trial (ACT14132) was reviewed by the FDA to assess safety of avalglucosidase alfa for use in IOPD patients who experienced clinical decline or were unresponsive to at least 6 months of alglucosidase therapy.[1] Secondary objectives of the study were to determine the effect of avalglucosidase alfa treatment on functional improvements and health-related quality of life as assessed through echocardiography, the Pompe-PEDI, and other measurement tools.[1] Enrolled patients included males and females <18 years of age (mean 6.7 years; range 1 to 12 years) with confirmed GAA enzyme deficiency and cardiomyopathy at time of diagnosis who had been receiving a consistent stable dose of alglucosidase alfa (between 20 mg/kg and 40 mg/kg) for at least 6 months immediately before trial entry. Initially, 11/22 patients were given avalglucosidase alfa at 20 mg/kg (n=6) or 40 mg/kg (n=5) for 6 months.[1] After the highest tolerated dose of avalglucosidase alfa was determined, the remaining 11 patients entered a separate cohort and were randomized 1:1 to be given avalglucosidase alfa 40 mg/kg (n=5) or maintain their stable dose of alglucosidase alfa (n=6) for 6 months.[1] The FDA determined that there was insufficient evidence of avalglucosidase alfa efficacy in the IOPD population due to inadequate sample size and high data variability.[1]

Without evidence of avalglucosidase alfa efficacy in LOPD patients less than 16 years of age, the FDA allowed the manufacturer to conduct a simulation based on pharmacokinetic (PK) data in order to determine whether the 20 mg/kg dose was appropriate across different ages or body weights.[1] It was reported that for the 20 mg/kg dose, patients with lower body weights tended to have lower area under the concentration-time curve over the first two weeks (AUC_{2w}) exposure than patients with higher body weight.[1] Therefore, it was argued that pediatric patients with lower body weights likely needed a higher dose to achieve a comparable exposure to adult patients.[1] The FDA also used safety data from study ACT14132 (see **Clinical Safety** section) in patients aged 1 to 11 years with IOPD to consider for approval in pediatric patients with LOPD, as it was determined that patients with IOPD were more severely affected, treatment-experienced, and received higher doses of avalglucosidase alfa over an adequate period of time.[1] Therefore, the incorporation of safety data from IOPD patients along with PK extrapolation based on modeling and simulation was the method employed to select the 40 mg/kg dosing regimen for pediatric patients with LOPD 1 year of age or older weighing <30 kg.

The clinical trials involved small numbers of subjects with mild disease manifestations and did not include patients with severe mobility issues, cardiac hypertrophy, or ventilator dependence. Baseline imbalances in patient characteristics were observed between the 2 groups. Notably, patients in the avalglucosidase group had slightly higher baseline mean/median percent predicted FVC, longer mean/median distance walked in the 6MWT (>20 m) and had (6-7%) less patients who required walking assistance devices than in the alglucosidase alfa arm. Although avalglucosidase alfa met criteria for non-inferiority compared to alglucosidase alfa, it is uncertain whether a 2.4% change in percent predicted FVC is clinically meaningful. It is also unclear why there was only a 0.5% change in percent predicted FVC in the alglucosidase alfa comparator given there was almost a 3% change vs placebo observed in previous trials. Similarly, with avalglucosidase alfa treatment, it is unclear if a 30-meter relative improvement in the 6MWT compared to alglucosidase alfa-treated patients represents a clinically meaningful difference in Pompe disease outcomes. In the Pompe disease (LOTS) trial, it was reported that alglucosidase-treated patients achieved 25 meters on the 6MWT but, in this study, (COMET) it was only 2 meters.[1,25] There was no explanation as to why only about half the patients crossed over to avalglucosidase alfa in the open-label extension trial were available for outcome assessment. With details regarding trial methods absent until the full study is published it is not possible to ascertain to what extent sources of bias such as concealment of allocation and blinding could affect the validity of the results. In addition, high dose avalglucosidase alfa (40 mg/kg) for LOPD patients <30kg was based on a manufacturer-derived model and indirect evidence. The FDA concluded that more long-term data is necessary to determine whether patients treated with avalglucosidase alfa will experience a decline in effectiveness over time similar to alglucosidase alfa or whether initial gains with treatment will persist beyond 2-3 years.[1] With a primary study population of 100 patients dispersed among 69 centers in 26 countries, it is unlikely that adequate oversight and standardized practices could be fully achieved. The small sample size and underrepresentation of minorities further limits the applicability of results to the general Oregon Medicaid population.

Clinical Safety:
There were 138 patients in the avalglucosidase alfa combined safety population, 119 who were age 16 or older with LOPD and 19 patients ages 1 to 11 years old with IOPD. Overall, 91% of these patients had treatment emergent adverse events (TEAEs) with nasopharyngitis (30%) identified as the most common. Moderate to severe adverse events (SAEs) were present in 91/138 (66%) of patients 1 of which was associated with a fatal outcome. Four patients (3%) had an adverse event which lead to discontinuation.

In the comparative efficacy trial (EFC14028), at least 1 or more TEAEs were reported by 44 (86%) of the patients treated with avalglucosidase alfa compared to 45 (92%) of the patients treated with alglucosidase alfa.[1] The most common TEAEs in the avalglucosidase alfa group compared to alglucosidase were influenza (18% vs 4%, respectively) and back pain (24% vs. 10%, respectively).[1] Sixteen patients (31%) who received avalglucosidase alfa had IARs compared to 23 (46%) who received alglucosidase alfa.[1] Three of the IARs in avalglucosidase alfa treated patients were categorized as severe reactions.[1] Four patients on avalglucosidase alfa and two on alglucosidase alfa experienced anaphylaxis during the primary analysis period.[1] The most common adverse events that occurred during treatment over 49 weeks in the avalglucosidase and alglucosidase groups, respectively, were headache (22% vs. 33%), fatigue (18% vs. 14%), diarrhea (12% vs. 16%), nausea (12% vs. 14%), arthralgia (10% vs. 16%), dizziness (10% vs. 8%), and myalgia (10% vs. 14%).[1,2] The adverse reactions reported during the Study 1 are summarized in **Table 3**.

Table 3. Adverse events occurring in more than 10% of patients treated with avalglucosidase alfa compared to alglucosidase alfa in Study 1 [1,2]

Adverse reaction	Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
Headache	22%	33%
Fatigue	18%	14%
Diarrhea	12%	16%
Nausea	12%	14%
Arthralgia	10%	16%
Dizziness	10%	8%
Myalgia	10%	14%

In the ACT14132 study (n=11), all patients in the avalglucosidase alfa and alglucosidase alfa groups reported TEAEs. TEAEs reported in the highest frequency among avalglucosidase alfa compared to alglucosidase groups were cough, device occlusion, diarrhea, eye irritation, headache, tachypnea, pyrexia, rhinorrhea, upper respiratory infection (URI), rash, and vomiting (40% vs 0% for all, respectively). Essentially all TEAEs were observed in the high-dose avalglucosidase alfa (40 mg/kg) group. No SAEs were determined to be related to avalglucosidase alfa therapy and no deaths occurred in the ACT14132 study.

FDA labeling has a BBW for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions and risk of acute cardiorespiratory failure in susceptible patients with avalglucosidase alfa infusions. Increased incidence of hypersensitivity reactions was observed in patients with higher anti-avalglucosidase alfa antibodies (antidrug antibodies, ADA).[2] The warning also cautions that patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.[2] Also, patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during avalglucosidase alfa infusion.[2] Patients with an acute underlying illness at the time of avalglucosidase alfa infusion may be at greater risk for IARs.[2] The FDA labeling suggests more frequent monitoring of vital signs should be performed during infusion in these susceptible patients, and in the event of a severe IAR, therapy should be immediately discontinued and appropriate medical treatment initiated.[2]

Look-alike / Sound-alike Error Risk Potential: No results identified.

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) Mean change in percent predicted FVC

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

Parameter	
Mechanism of Action	Avalglucosidase alfa is an exogenous source of the GAA, which is required for glycogen cleavage. Due to an inherited GAA deficiency or absence, glycogen accumulates in the tissues of patients with Pompe disease. Mannose-6-phosphate on avalglucosidase alfa mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported to lysosomes where it is activated for increased enzymatic glycogen cleavage.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd: 3.4 L; Protein binding is unknown
Elimination	Not reported
Half-Life	1.6 hours
Metabolism	Metabolized into small peptides and amino acids via catabolic pathways

Abbreviations: GAA=acid alpha-glucosidase; L=liters; N/A=not applicable; Vd=volume of distribution; 6MP=Mannose-6-phosphate.

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. Study 1 (COMET) Phase 3, MC, DB, RCT [1,2]	1. Avalglucosidase alfa: 20 mg/kg every other week (n=51) 2. Alglucosidase alfa: 20 mg/kg every other week (n=49)	Demographics: -Mean Age: 48 years (range 16 to 78 yrs) -Male: 52% -Race: White (94%) -FVC % predicted: 63% -Distance 6MWT: 389 meters Key Inclusion Criteria: Males and females with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed GAA gene variants Key Exclusion Criteria: -Age <3 years.	ITT: 1. 51 2. 49 Attrition: 1. 0 2. 5	Primary Endpoint: Changes from Baseline to Week 49 in upright FVC % predicted were numerically greater with avalglucosidase alfa-ngpt vs. alglucosidase alfa 1. 2.89 ± 0.88% (95% CI, 1.13 to 4.65) 2. 0.46 ± 0.93% (95% CI, −1.39 to 2.31) LSM±SE difference: 2.43% (95% CI, −0.13 to 4.99; p=0.0626) Noninferiority margin = −1.1: avalglucosidase alfa-ngpt noninferior to alglucosidase alfa (p=0.0074) Secondary Endpoints:	N/A for all	Any TEAE 1. 44 (86%) 2. 45 (92%) Treatment-related TEAE: 1. 23 (45%) 2. 24 (49%) SAEs: 1. 8 (16%) 2. 12 (25%) AE leading to discontinuation of study drug: 1. 0 2. 4 (8%)		**Risk of Bias (low/high/unclear)**: FDA approval was based on one unpublished study. Risk of bias cannot be fully assessed. **Applicability**: Patient: LOPD in patients over 16 years without prior ERT. Most patients were between 16 to 78 years of age. Intervention: Avalglucosidase alfa at fixed dose intervals Comparator: Alglucosidase alfa Outcomes: % predicted FVC; 6MWT; Physical and mental QoL assessments via SF-12 Setting: 69 centers in 26 countries

		-cardiac hypertrophy -Wheelchair dependence (inability to ambulate 40 meters) -Dependence on invasive ventilation (noninvasive ventilation allowed) -Inability to perform repeated FVC measurements in upright position of ≥30% to ≤85% predicted -Previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease. -Prior or current use of ITI therapy		6MWT change from baseline: 1. 32.21 ± 9.93 m 2. 2.19 ± 10.40 m LSM±SE difference: 30.01 m (95% CI, 1.33 to 58.69); p=0.0405 SF-12 (PCS and MCS) change from baseline: No difference between groups				
Abbreviations: 6MWT = six-minute walk test; AE = adverse events CI = confidence interval; DB = double-blind; ERT = enzyme replacement therapy; GAA=enzyme acid alpha-glucosidase; FVC = forced vital capacity; ITI = immune tolerance induction; ITT = intention to treat; LOPD = late-onset Pompe disease; LSM = least squares mean; MHC = mental health component summary; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PCS = physical component summary; PP = per protocol; RCT = randomized-controlled trial; TEAE = treatment emergent adverse events; SAE = serious adverse events; SF12 = short form twelve								

References:

1. FDA Center for Drug Evaluation and Research. Nexviazyme Integrated review. Application number761194. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761194#collapseApproval
2. Nexviazyme (avalglucosidase alfa) Prescribing Information. Genzyme Corp. Cambridge, MA; Aug. 2021.
3. Chen M, Zhang L, Quan S. Enzyme replacement therapy for infantile-onset Pompe disease. *Cochrane Database of Systematic Reviews*. 2017;2017(11).
4. van der Ploeg AT, Reuser AJJ. Pompe's disease. *The Lancet*. 2008;372(9646):1342-1353.
5. Ferreira CR, Gahl WA. Lysosomal storage diseases. *Translational science of rare diseases*. 2017;2(1-2):1-71.
6. Burton BK, Charrow J. Newborn screening for lysosomal storage disorders in Illinois: The initial 15-month experience. *J Pediatr* 2017; 190: 130-135.
7. Hopkins, PV, Klug, T. Incidence of 4 lysosomal storage disorders from 4 years of newborn screening. JAMA Pediatr 2018; 172(7): 696-697.
8. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated 2017 May 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2021.
9. Oregon Health Authority, Public Health Division. Oregon State Public Health Laboratory, Newborn Screening Letter. 9/1/2018 https://www.oregon.gov/oha/PH/LABORATORYSERVICES/NEWBORNSCREENING/Pages/index.aspx Accessed 11/2/2021.
10. American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. *Muscle Nerve.* 2009;40(1):149-160.
11. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline [published correction appears in *Genet Med.* 2006 Jun;8(6):382. ACMG Work Group on Management of Pompe Disease [removed]; Case, Laura [corrected to Case, Laura E]]. *Genet Med.* 2006;8(5):267-288.
12. Chan J, Desai AK, Kazi ZB, et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review. *Mol Genet Metab* 2017;120(3):163–172.
13. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve.* 2012;45(3):319-333. doi:10.1002/mus.22329
14. Kroos M, Hoogeveen-Westerveld M, van der Ploeg A, et al. The genotype-phenotype correlation in Pompe disease. *Am J Med Genet C: Semin Med Genet* 2012;160(1):59–68.
15. Shieh JJ, Lin CY. Frequent mutation in Chinese patients with infantile type of GSD II in Taiwan: evidence for a founder effect. *Hum Mutat* 1998;11(4):306–312.
16. Becker JA, Vlach J, Raben N, et al. The African origin of the common mutation in African American patients with glycogenstorage disease type II. *Am J Hum Genet* 1998;62(4):991–994.
17. Esmer C, Becerra-Becerra R, Peña-Zepeda C, Bravo-Oro A. A novel homozygous mutation at the GAA gene in Mexicans with early-onset Pompe disease. *Acta Myol*. 2013;32(2):95-99.
18. Huie ML, Hirschhorn R, Chen AS, et al. Mutation at the catalytic site (M519V) in glycogen storage disease type II (Pompe disease) *Hum Mutat.* 1994;4:291–293.
19. Labrousse P, Chien YH, Pomponio RJ, et al. Genetic heterozygosity and pseudodeficiency in the Pompe disease newborn screening pilot program. *Mol Genet Metab* 2010;99(4):379–383.
20. Kumamoto S, Katafuchi T, Nakamura K, et al High frequency of acid alpha-glucosidase pseudodeficiency complicates newborn screening for glycogen storage disease type II in the Japanese population. *Mol. Genet. Metab.,* 97 (2009), pp. 190-195
21. Lim J-A, Li L, Raben N. Pompe disease: from pathophysiology to therapy and back again. *Front Aging Neurosci.* 2014;6:177-177.

22. Laukkanen JA, Khan H, Kurl S, et al. Left ventricular mass and the risk of sudden cardiac death: a population-based study. *Journal of the American Heart Association.* 2014;3(6):e001285-e001285.
23. Harlaar L, Hogrel J-Y, Perniconi B, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology*. 2019;93(19):e1756-e1767.
24. Kishnani PS, Goldenberg PC, DeArmey SL, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab*. 2010;99(1):26-33.
25. FDA Center for Drug Evaluation and Research. Lumizyme Multi-Discipline Review. Application Number 125291Orig1s136. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125291s000TOC.cfm.
26. Finkleman FD, Madden KB, Morris SC, et al. Anti-cytokine antibodies in carrier proteins. *J Immun.* 1993. 151: 1235-1244.
27. FDA Center for Drug Evaluation and Research. Myozyme Multi-Discipline Review. Application Number 125141s000. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125141s000_MyozymeTOC.cfm
28. Lumizyme (alglucosidase alfa) Prescribing Information. Genzyme Corp. Cambridge, MA; Feb. 2020.
29. van der Ploeg AT, Kruijshaar ME, Toscano A, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. *Eur J Neurol.* 2017;24(6):768-e31.
30. ATS/ERS Statement on Respiratory Muscle Testing. *American Journal of Respiratory and Critical Care Medicine*. 2002;166(4):518-624.
31. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH: Interpreting small differences in functional status: the Six Minute Walk Test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997, 155:1278–1282.
32. Ware JE Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998;51:903–912.
33. Gandek B, Ware JE, Aaronson NK, et al. Cross-Validation of Item Selection and Scoring for the SF-12 Health Survey in Nine Countries: Results from the IQOLA Project. *Journal of Clinical Epidemiology*. 1998;51(11):1171-1178.
34. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better? *Orphanet J Rare Dis.* 2013;8:160-160.
35. Tarnopolsky M, Katzberg H, Petrof BJ, et al. Pompe Disease: Diagnosis and Management. Evidence-Based Guidelines from a Canadian Expert Panel. *Can J Neurol Sci.* 2016;43(4):472-485.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
alglucosidase alfa	LUMIZYME	VIAL	N
avalglucosidase alfa-ngpt	NEXVIAZYME	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to November 05, 2021>

1. Pompe disease.mp. or Glycogen Storage Disease Type II/ 2284
2. alglucosidase.mp. / 152
3. avalglucosidase.mp. / 4
4. 2 or 3/ 155
5. 1 and 4/ 141
6. limit 5 to (english language and humans and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))/ 28

Appendix 3: Prescribing Information Highlights

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

NEXVIAZYME (avalglucosidase alfa-ngpt) for injection, for intravenous use
Initial U.S. Approval: 2021

WARNING: SEVERE HYPERSENSITIVITY REACTIONS, INFUSION-ASSOCIATED REACTIONS, and RISK OF ACUTE CARDIORESPIRATORY FAILURE IN SUSCEPTIBLE PATIENTS

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions Including Anaphylaxis

- **Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. (5.1)**

Infusion-Associated Reactions (IARs)

- **If severe IARs occur, consider immediate discontinuation and initiation of appropriate medical treatment. (5.2)**

Risk of Acute Cardiorespiratory Failure in Susceptible Patients

- **Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during NEXVIAZYME infusion. (5.3)**

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

NEXVIAZYME is a hydrolytic lysosomal glycogen-specific enzyme indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). (1)

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

- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to NEXVIAZYME administration to reduce the risk of IARs. (2.1)
- Must be reconstituted and diluted prior to use.
- See full prescribing information for administration instructions including the recommended infusion rate schedule. (2.1, 2.3, 2.4)
- NEXVIAZYME is administered as intravenous infusion. For patients weighing (2.1):
  - ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks.
  - <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks.
- See the full prescribing information for dosage modifications due to hypersensitivity reactions or IARs. (2.2)

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

For injection: 100 mg of avalglucosidase alfa-ngpt as a lyophilized powder in a single-dose vial for reconstitution. (3)

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

None. (4)

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

See boxed warning. (5.1, 5.2, 5.3)

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

The most common adverse reactions (>5%) were headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia and urticaria. (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: 8/2021

Pompe Disease

Goal(s):
- Ensure medically appropriate use of approved agents for the treatment of Pompe disease

Length of Authorization:
- Up to 12 months

Requires PA:
- Alglucosidase alfa (pharmacy and physician administered claims)
- Avalglucosidase 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

Agent	Indication	Age Minimum	Dosing Regimen
Alglucosidase alfa	Early Onset Pompe Disease (EOPD) Late Onset Pompe Disease (LOPD)	None	20 mg/kg IV once every 2 weeks
Avalglucosidase alfa	Late Onset Pompe Disease (LOPD)	≥ 1 year	< 30 kg: 40 mg/kg IV once every 2 weeks
			≥ 30 kg: 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.

Approval Criteria		
3. Is the requested agent for an approved indication and dosed appropriately based on age and weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #4. Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is there documentation that the patient is switching enzyme replacement therapy (ERT) agents due to lack of benefit with prior therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Does the patient have signs or susceptibility to any of the following? • Fluid volume overload • Acute underlying respiratory illness • Compromised cardiac or respiratory function necessitating fluid restriction	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
7. 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 #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the request for treatment of late-onset Pompe disease (LOPD)?	**Yes:** Go to #13	**No:** Go to #10
10. 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 (e.g. FEV or other age-appropriate test of pulmonary function)? • Cardiac imaging (e.g. chest x-ray, echocardiography)? • CRIM status?	**Yes:** Document baseline results and go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient CRIM-negative?	**Yes:** Go to #12	**No:** Approve for 3 months If approved, a referral will be made to case management by the OHA.
12. 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
13. Is the patient 5 years of age or older?	**Yes:** Go to #14	**No:** Go to #15
14. 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 OHA.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
15. Has the provider documented a baseline value for both of the following assessments: • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status (e.g. FEV or other age-appropriate test of pulmonary function)?	**Yes:** Approve for 3 months Document baseline results. If approved, a referral will be made to case management by OHA.	**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 a request for **al**glucosidase alfa?	**Yes:** Go to #3	**No:** Go to #5
3. Is this the first renewal for **al**glucosidase alfa?	**Yes:** Go to #4	**No:** Go to #5
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is patient under 5 years old?	**Yes:** Approve for 3 months	**No:** Go to #7

Renewal Criteria		
7. Has the patient received the requested therapy for at least 6 months?	**Yes:** Approve for 12 months	**No:** Approve for 3 months

P&T/DUR Review: 2/22 (DE); 4/21 (DE); 2/22 (DE)
Implementation: TBD; 5/1/21; 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 Update with New Drug Evaluation: Immunosuppressants

Date of Review: February 2022

Date of Last Review: February 2020
Dates of Literature Search: 10/31/2019 - 09/16/2021
Brand Name (Manufacturer):
Lupkynis™ (Aurinia Pharmaceuticals, Inc.)
Saphnelo™ (AstraZenica)
Dossier Received: yes

Generic Name:
Voclosporin
Anifrolumab-fnia

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

Purpose for Class Update:
The purpose of this class update is to evaluate new comparative evidence for efficacy and safety of immunosuppressants, and to evaluate place in therapy belimumab (newly expanded indication for lupus nephritis [LN]), voclosporin (recently approved for lupus nephritis) and anifrolumab-fnia (recently approved for treatment of systemic lupus erythematosus [SLE]).

Research Questions:
1. Is there new comparative evidence that immunosuppressants differ in efficacy or effectiveness?
2. Is their new comparative evidence that immunosuppressants differ in safety?
3. What is the evidence for belimumab and voclosporin in LN?
4. What is the evidence for anifrolumab-fnia in SLE?
5. Are there specific subpopulations (age, race, ethnicity, gender, diagnosis, disease severity, and comorbidity) for which some immunosuppressants have different effectiveness or safety than other immunosuppressants?

Conclusions:
- Five high quality systematic reviews, 4 clinical practice guidelines, 3 new randomized controlled trials, 1 new formulation, 1 new indication, and 1 safety alert were identified after literature review to update evidence for this class.
- High quality guidelines and systematic reviews support the Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug placement for the currently preferred agents.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Based on findings from a Drug Effectiveness Review Project report, there is low quality evidence that belimumab is more likely to achieve complete renal response (CRR) or primary efficacy renal response (PERR) than placebo at week 104 in patients with Class III, Class IV, or Class V (in combination with Class III or IV) LN based on 2 randomized controlled trials (RCTs)[1]:
    - CALIBRATE (n=33, background therapy rituximab + cyclophosphamide , moderate risk of bias [RoB]): CRR week 48, belimumab 38.0% vs. placebo 31.8%, 95% confidence interval (CI) -23.4% to 32.5%, P=0.76; CRR week 96, 23.8% vs 18.2%, 95% CI -18.7% to 30.0%, P=0.67.
    - BLISS-LN (n=446, background therapy randomized to cyclophosphamide plus azathioprine, or mycophenolate mofetil [MMF], moderate RoB):
        - PERR week 104, belimumab 43.0% vs. placebo 32.3%, hazard ratio (HR) 1.46, 95% CI 1.07 to 1.98, P=0.02, absolute risk reduction (ARR) 10.8%, number needed to treat (NNT) 10.
        - CRR week 104, belimumab 30.0% vs. placebo 19.7%, relative risk (RR) 1.52, 95% CI 1.09 to 2.12, P=0.01, ARR 10.3%, NNT 10.
    - BLISS-LN cyclophosphamide plus azathioprine background therapy subgroup: no significant differences in reaching PERR or CRR at week 104 with belimumab vs. placebo
    - BLISS-LN MMF background therapy subgroup:
        - PERR at week 104, belimumab 46.3% vs. placebo 34.1%, Odds Ratio (OR) 1.58 95% CI, 1.00 to 2.51
        - CRR at week 104, belimumab 34.1% vs. placebo 20.1%, OR 2.01, 95% CI 1.19 to 3.38
    - Infectious related treatment emergent adverse events (TEAEs) were the most common in all groups. The most frequent infection-related TEAEs in both groups were upper respiratory tract infection (URTI), urinary tract infection (UTI), herpes zoster, bronchitis, and nasopharyngitis.
- Based on findings from a Drug Effectiveness Review Project report, there is low quality evidence that *low dose* voclosporin 23.7 mg twice daily is superior to placebo at achieving CRR at 24 to 52 weeks based on 2 RCT with background therapy of MMF (corticosteroid use varied by protocol) in patients with Class III, Class IV-S or IV-G (A or A/C) or Class V alone or in combination with Class III or IV LN[1]:
    - AURA-LV (n=265, high RoB):
        - CRR week 24, low dose voclosporin 23.7 mg twice daily 32.6% vs. placebo 19.3%, RR 1.69, 95% CI 1.00 to 2.84, P=0.046, ARR 13.3%, NNT 8. High dose voclosporin 39.5 mg twice daily not significant vs. placebo, P=0.22.
        - CRR week 48, low dose voclosporin 49.4% vs. placebo 23.9%, RR 2.07, 95% CI 1.35 to 3.18, P<0.001, ARR 25.6%, NNT 4. High dose voclosporin 39.8% vs. placebo 23.9%, RR 1.67, 95% CI 1.06 to 2.62, P=0.02, ARR 15.9%, NNT 7.
    - AURORA A (n=357, moderate RoB):
        - CRR week 52, low dose voclosporin 40.8% vs. placebo 22.5%, RR 1.81, 95% CI 1.31 to 2.51, P<0.001, ARR 18.3%, NNT 6.
        - CRR week 24, low dose voclosporin 32.4% vs. placebo 19.7%, RR 1.65, 95% CI 1.14 to 2.37, P=0.006, ARR 12.7%, NNT 8.
    - The most frequent TEAEs were infections and infestations, gastrointestinal disorders, nervous system disorders, and renal and urinary disorders.
- There is insufficient evidence from 3 RCTs (one phase 2b, two phase 3) that anifrolumab-fnia 300 mg intravenously (IV) reduces SLE disease activity at 24 to 52 weeks in patients with moderate to severe SLE.[2-4] Evidence was downgraded due to risk of bias, imprecision, and indirectness.
    - MUSE had a statistically significant Systemic Lupus Erythematosus Responder Index (SRI-4) response with glucocorticoid (GC) tapering in the anifrolumab-fnia 300 mg dose group compared to placebo at week 24 (anifrolumab-fnia 300 mg 34.3% vs. placebo 17.6%; OR 2.38, 95% CI 1.19 to 4.77; NNT 6) and at week 52 (anifrolumab-fnia 300 mg 51.5% vs. placebo 25.5%; OR 3.08, 90% CI 1.86 to 5.09, P<0.001). The prespecified use of the high type I interferon (IFN) subpopulation at week 24 showed similar results (anifrolumab-fnia 300 mg 36.0% vs. placebo 13.2%; OR 3.55, 95% CI 1.5 to 7.32; NNT 5). MUSE used a type 1 error rate of 0.1 (two-sided).
    - TULIP-1 failed to find statistical significance for the primary endpoint of SRI-4 response at 52 weeks at either anifrolumab-fnia dose (anifrolumab-fnia 300 mg 36.1% vs. placebo 40.2%; -4.2% difference, 95% CI -14.20 to 5.82, P=0.41). TULIP-1 used BICLA (British Isles Lupus Assessment Groups Index

[BILAG]-based Combined Lupus Assessment) as a secondary endpoint (anifrolumab-fnia 300 mg 37.2% vs. placebo 26.6%; 10.6% absolute difference, 95% CI 0.59 to 19.68).
    - TULIP-2 changed the primary outcome via protocol amendment after TULIP-1 failed to find statistical significance. The change occurred after discussion with the FDA and experts and prior to data unblinding or analysis. TULIP-2 had a statistically significant difference in BICLA response at 52 weeks (anifrolumab-fnia 300 mg 47.8% vs. placebo 31.5%; 16.3% difference, 95% CI 6.3 to 26.3, P=0.001; NNT 7).
    - Complete improvement in a single organ system is needed to achieve SRI-4 response, while partial improvement in multiple affected systems may achieve BICLA response.[5] In real world data comparing these composite endpoints to clinician's global rating of improvement the BICLA was less sensitive than SRI, especially in patients with baseline involvement of multiple organs (**Table 3**).[6]
    - Infections including upper respiratory tract infection and bronchitis are the most common TEAE observed with anifrolumab-fnia. Hypersensitivity and severe infusion related reactions are possible with monoclonal antibody administration.
- Outcome conclusions specific to race and ethnicity are insufficient due to variations of results, lack of statistical significance with many comparisons, and small subgroup sizes. Men are generally underrepresented due to reduced incidence of SLE in men, despite much higher propensity to develop LN.[1] Safety in pregnancy and pediatric patients is unclear for all three drugs.

Recommendations:
- No Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug list (PDL) changes are recommended to the Immunosuppressant class or belimumab based on clinical evidence.
- Update belimumab prior authorization (PA) criteria.
- Implement PA for voclosporin to ensure appropriate use in FDA-approved indications funded by OHP.
- Implement PA for anifrolumab-fnia to ensure appropriate use in FDA-approved indications funded by OHP.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- Previous review of evidence found clinical remission in Crohn's disease more effective in patients with infliximab compared to azathioprine, and combination was more effective than infliximab alone. In patients undergoing kidney transplant, mycophenolate mofetil (MMF) was more effective at preserving graft function and preventing acute rejection than azathioprine, but cytomegalovirus (CMV) was more common with MMF.
- High quality guidelines support the OHP FFS preferred drug placement for the treatment of Crohn's disease, kidney transplant, and ulcerative colitis.
- No changes to the PDL were recommended based on the evidence.
- After evaluation of costs in executive session and consideration of high approval percentage of current prior authorization requests, all medications in this class were made PDL preferred.
- Prior Authorization update of belimumab was approved by the Pharmacy and Therapeutics (P & T) committee in August 2021 for the expanded FDA indication for treatment of adults with active LN. Belimumab is in the "Targeted Immune Modulators" class in the OHP FFS PDL (Appendix 1).

Background:
Immunosuppressive agents can be used to treat and manage a wide range of conditions, including patients with graft-versus-host disease, rejection prophylaxis in solid organ transplant recipients, and myasthenia gravis. The primary focus of this review is to evaluate evidence related to new agents for treatment of SLE and its complications, specifically LN.

Systemic lupus erythematosus is a chronic multisystem autoimmune disorder of the connective tissue which causes significant morbidity and mortality in the United States (U.S.) and worldwide. Estimates on prevalence vary based on changing detection methods and case definitions over time. Estimates may also vary based on genetic and environmental differences between countries.[6] Research studies conducted within the past 2 decades have prevalence estimates of 9 to 241 per 100,000 person-years and an incidence of 0.3 to 23.2 per 100,000 person-years.[6] Data from studies conducted within the U.S. population with better designs involving strict case definitions, broad case-finding methodology, and correcting for possible case under-ascertainment show incidence of 4.6 to 6.4 per 100,000 person years and prevalence of 62.2 to 84.8 per 100,000 person years.[6] The Centers for Disease Control and Prevention estimates a U.S. prevalence of 322,000 probable or definite SLE cases.[7] Rates are generally higher among non-Whites, including both Hispanic and Arab ethnicities and those with American Indian, Alaska native, South/East Asian, and African descent.[6] Hispanic and South/East Asian individuals may have more severe disease and organ damage.[1,6] People of African descent are three times more likely to be afflicted with SLE, and have higher rates of renal involvement and mortality than Whites.[6,7] European ancestry is associated with a lower risk of LN.[6] While some of these differences may have genetic components, it has been shown that lower socioeconomic status, educational level, and poverty are associated with the health disparities of higher disease activity, organ damage, and mortality.[6]

Females in their reproductive years are most commonly afflicted with SLE.[1,6] The female-to-male ratio is estimated at 7 to 15:1 in adults and 3 to 5:1 in children. Disease onset in women is usually the 3rd to 5th decade of life; it generally presents later in men in the 5th to 7th decade. While representing about 1 in 10 SLE diagnoses, men tend to develop more severe disease and are 66% more likely to be diagnosed with LN than women based on U.S. Medicaid data.[1]

Smoking, endometriosis, alcohol consumption, and inhalational silica exposure have been strongly associated with SLE.[6] Additionally, psychological stress and environmental triggers such as ultraviolent light, certain drugs (echinacea, trimethoprim/sulfamethoxazole), infections, and mercury have been implicated.[7] The possible role of the gut microbiome is also under investigation.[6]

Systemic lupus erythematosus results from disruption of both the innate and adaptive arms of the immune system.[7] SLE patients have variable presentation, prognosis, and experience remissions and flares over the course of disease.[8] Many different organs are attacked by autoantibodies produced by the body, and this results in variety of complications.[1] Cutaneous lupus presents in nearly 90% of patients, and may manifest in an acute, subacute, or chronic fashion.[7] Non-lupus specific manifestations such as alopecia, vasculitis, livedo reticularis, periungual telangiectasias, and Raynaud's phenomenon may be present.[7] Musculoskeletal involvement is very common and arthralgia and true synovitis occur for almost 90% of patients. Renal disease and central nervous system disease are both associated with significant complications.[7] Kidney disease, present in 50% of patients, is a major cause of morbidity and mortality. The delayed diagnosis of LN is a major risk factor for end-stage-renal disease (ESRD).[7] Prevalence of LN varies within US; among Medicaid beneficiaries LN is two times more common in the South.[1] Childhood-onset of SLE is associated with higher incidence and more severe LN than adult-onset disease.[9] Cognitive impairment is present is nearly 80% of SLE patients.[7] Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state are associated with SLE and may assist with diagnosis once other causes are excluded.[7] Patients with SLE are at higher risk of cardiovascular disease, and 10-15% of SLE cases are complicated by antiphospholipid syndrome. Pregnancy in patients with SLE is associated with higher rates of preterm birth, pre-eclampsia, and caesarean section. Prenatal planning and antenatal care are necessary to reduce the risk of complications to both parent and child.[7] Malignant disorders are more common in SLE patients.[6,9] Hospitalization rates due to infection, most commonly pneumonia, are twelve times higher in patient with SLE than those without, though the specific drug classes used for treatment of SLE are further risk factors for infectious complications.[6] Long-term use of steroids can also put SLE patients at risk of bone loss and fractures.[9]

Diagnosis of SLE is made using clinical manifestations and positive serologies.[7,8,10] The European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019 and Systemic Lupus International Collaborating Clinics (SLICC) 2012 both have classification criteria for SLE.[8,10] The more recent EULAR/ACR criteria are frequently used in practice (**Table 1**). Patients who meet the entry criterion of a positive antinuclear antibody (ANA) proceed to assessment of additive criteria. Patients with at least one clinical criteria without a more likely explanation, and a score of ≥ 10 points meet criteria for SLE diagnosis.[10]

Table 1. European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019 Diagnostic Criteria[10]

Entry criterion Antinuclear antibodies at a titer of ≥ 1:80 on HEp-2 cells or an equivalent positive test ever in lifetime			
↓			
If absent, do not classify as systemic lupus erythematosus If present, apply additive criteria			
↓			
Additive criteria Do not count a criterion if there is a more likely explanation than systemic lupus erythematosus Occurrence of a criterion on a least one occasion is sufficient SLE classification requires at least one clinical criterion and ≥ 10 points Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total scores.*			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional • Fever	2	***Antiphospholipid antibodies*** • Anti-cardiolipin antibodies OR • Anti-beta2GP1 antibodies OR • Lupus anticoagulant	2
Hematologic • Leukopenia • Thrombocytopenia • Autoimmune hemolysis	3 4 4	***Complement proteins*** • Low C3 OR low C4 • Low C3 AND low C4	3 4
Neuropsychiatric • Delirium • Psychosis • Seizure	2 3 5	***SLE-specific antibodies*** • Anti-dsDNA antibody† OR • Anti-Smith antibody	6
Mucocutaneous • Non-scarring alopecia	2		

• Oral ulcers • Subacute cutaneous OR discoid lupus • Acute cutaneous lupus	2 4 6	
Serosal • Pleural or pericardial effusion • Acute Pericarditis	 5 6	
Musculoskeletal • Joint involvement	 6	
Renal • Proteinuria >0.5g/24 h • Renal biopsy Class II or V lupus nephritis • Renal biopsy Class III or IV lupus nephritis	 4 8 10	
Total Score: If entry criterion fulfilled and score of 10 or greater should be classified as systemic lupus erythematosus		
* Additional criteria within the same domain will not be counted † Using assay with 90% specificity against relevant disease controls		

Lupus nephritis diagnosis is generally confirmed through kidney biopsy. Serum creatine, urinalysis, spot protein-creatinine ratio, and serology (including anti-dsDNA and complement) are recommended in patients at SLE presentation and times of suspected SLE flare. Evidence of abnormal protein/urine sediment or decreased/decreasing glomerular filtration rate (GFR) should be further evaluated to quantify proteinuria or accuracy of GFR results. Patients with 24-hour proteinuria ≥ 0.5 g/24h or abnormal eGFR with no attributable cause other than SLE should be considered for kidney biopsy.[9]

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system is most commonly used for LN (**Table 2**).[11] Disease classes are based on glomerular pathology ranging from class I, demonstrating minimal mesangial LN, to Class VI, demonstrating advanced sclerosis LN with ≥ 90% of glomeruli globally sclerosed without residual activity. Class III focal lupus nephritis and class IV diffuse lupus nephritis include additional subcategories for the presence of lesions which are active, active and chronic, or inactive and chronic. Additionally, classifications can differentiate segmental versus global lesions. Tubular atrophy, interstitial inflammation and fibrosis, and severity of arteriosclerosis or other vascular lesions should also be graded as mild, moderate, or severe.[8]

Table 2. ISN/RPS Lupus Nephritis Classifications[11]

Status	Description
Class I	Minimal mesangial lupus nephritis: earliest and mildest form of glomerular involvement
Class II	Mesangial proliferative lupus nephritis: excellent prognosis and no specific therapy is indicated
Class III	Focal lupus nephritis: patients present with hematuria and proteinuria, possibly to also have hypertension, decreased renal function and/or nephrotic syndrome. Light microscopy reveals less than 50 percent of glomeruli are affected.
Class IV	Diffuse lupus nephritis: patients present with hematuria and proteinuria and frequently seen with hypertension, decreased renal function and nephrotic syndrome. Light microscopy reveals more than 50 percent of glomeruli are affected.
Class V	Lupus membranous nephropathy: patients present with signs of nephrotic syndrome
Class VI	Advanced sclerosing lupus nephritis: patients present with slowly progressive kidney dysfunction associated with proteinuria

The goal of SLE treatment is to achieve remission or low disease activity.[12] Treatment of SLE for most patients involves use of hydroxychloroquine (HCQ), unless contraindicated, with the addition of GC at the lowest dose needed to enable remission or prevention of flares. Remission is characterized by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 0 (range 0 to 105)[6] on HCQ and without need for GC.[12] Administration of GC ranges from chronic therapy to high dose pulses for severe flares, and GC should be withdrawn whenever possible for stable disease. Immunosuppressive agents such as methotrexate, azathioprine, and MMF can be added in patients unresponsive to other therapies and those unable to achieve low daily GC doses (e.g. ≤ 7.5 mg/day). Intravenous cyclophosphamide can be considered as a rescue treatment in severe or life-threatening situations when disease is unresponsive to other therapies.[13] The biologic agents belimumab and rituximab have been considered in certain situations; use of rituximab for SLE is off-label, and there have been negative results in certain SLE RCTs.[12,13] Treatment for specific organ complications is dependent on the organ system involved.[12]

Treatment of LN rests in early recognition, followed by induction therapy with MMF or low-dose IV cyclophosphamide.[12] In those with high risk of renal failure, high-dose IV cyclophosphamide may also be considered. Maintenance therapy with MMF or azathioprine should begin after induction.[12] MMF can be combined with a low dose calcineurin inhibitor (CNI) (e.g. cyclosporine or tacrolimus; recommendation preceded FDA approval of voclosporin) in severe nephrotic syndrome or incomplete renal response in certain patients with absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.[12]

There remains uncertainty regarding the most appropriate endpoint to use for treatment response in SLE or LN, or clear minimally clinically important differences (MCID). The SLEDAI-2K and British Isles Lupus Assessment Groups Index (BILAG) are both designed to assess disease activity.[5] Systemic Lupus Erythematosus Disease Activity Measure (SLEDAI) is a global index developed in 1986 and has been modified into multiple versions. Scores range from 0 to 105 and those above 5 have a greater than 50% probability of initiating therapy.[14] Score ranges are: no activity (0), mild activity (1-5), moderate activity (6-10), high activity (11-19), and very high activity (≥ 20).[14] A modified version of SLEDAI, the SLEDAI-2K marks 24 manifestations in nine organ systems as present or absent in the previous 30 days.[14] It is a composite global disease activity index. It has been validated and is able to predict major outcomes (e.g. organ damage, mortality). In contrast, BILAG-2004 is a disease activity index using organ-based scales. BILAG scores 9 organ systems as new or recurring, worse, same, improving, or not present during the previous 30 days. Each organ is then assigned a grade of: A (major activity), B (intermediate activity), C (mild or stable disease), D (previous involvement but currently inactive), and E (no previous activity).[5,14] It is not widely used in practice.[6] Additionally, while it is a valid and reliable tool for assessing disease activity, use as a measure of treatment response in the clinical trial setting is an adaptation for which it was not designed.[5] The

Safety of Estrogen in Lupus Erythematosus National Assessment Group (SELENA), SELENA-SLEDAI, is able to count persistent active disease in some cutaneous manifestations.[6] It is a cumulative and weighted index to assess disease activity across 24 domains (e.g., seizure, fever) in individuals with lupus.[5]

SRI-4 and BICLA are composite endpoints used in these studies of potential SLE treatments which include multiple components of disease activity (**Table 3**). Both were developed specifically for clinical trials, SRI based on an exploratory analysis of a phase 2 belimumab trial, and BICLA as part of a phase 2B study for an experimental medication called epratuzumab.[6] Complete improvement in a single organ system is needed to achieve SRI-4 response, while partial improvement in multiple affected systems may achieve BICLA response.[5] In real world data comparing these composite endpoints to clinician's global rating of improvement the BICLA was less sensitive than SRI-4, especially in patients with baseline involvement of multiple organs.[6] These composite indices are also highly complex, which limits applicability to clinical practice, and complicates translation of clinical trial results to individual patients and their disease.[6] For LN, various combinations of "primary efficacy renal response" or "complete renal response" have been used in RCTs, usually including improvement to a specific threshold for urine protein to creatinine ratio (UPCR), percentage improvement in eGFR, and need for rescue therapy, but the values for these component measures are not standardized across RCTs.[1,6] There is no standard eGFR MCID in this population, though studies of graft failure in organ transplant patients have found 5 mL/min/1.73m^2 difference in 12-month eGFR to be associated with almost a 20% increase in death-censored graft failure risk.[1]

Table 3. Disease Activity Composite Endpoint Descriptions for SLE[6]

Composite Endpoint*	Component	Description
SRI-4	SELENA-SLEDAI[†]	Improvement (≥ 4 point reduction in score)
	BILAG-2004	No new A (active disease) domain score and no more than 1 new B (intermediate activity) domain scores
	PGA	No worsening (<0.3 point decrease on 3 point VAS)
BICLA responder index	BILAG-2004	Improvement with all A scores at baseline improved to B/C/D, and all B scores improved to C/D
	BILAG-2004	No worsening in disease activity with no new A scores and ≤ 1 new B scores
	SLEDAI-2K	No worsening of total score from baseline
	PGA	No worsening (<10% worsening in 100 mm visual analog PGA scale or <0.3 point decrease on 3 point VAS)
	No treatment failure	No new or increased immunosuppression or antimalarials, or increased parenteral corticosteroids, or premature discontinuation from study treatment

*Patients must meet all criteria to be considered a responder to treatment.
[†]SRI-4 originally designed and used SELENA-SLEDAI in a belimumab clinical trial.[6] SLEDAI-2K was substituted for SELENA-SLEDAI in Anifrolumab clinical trials described in this class update.[5]
Abbreviations: BICLA=BILAG-based Combined Lupus Assessment; BILAG=British Isles Lupus Assessment Groups Index; PGA=Physician Global Assessment; SELENA=Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SRI=Systemic Lupus Erythematosus Responder Index; VAS=visual analogue scale

There are fewer than 60 patients receiving prescriptions for immunosuppressive agents for any indication in the OHP FFS population.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness

Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:

Drug Review Effectiveness Project: Belimumab (Benlysta) and Voclosporin (Lupkynis™) for Active Lupus Nephritis[1]

A review of the use of belimumab and voclosporin was completed by the Drug Review Effectiveness Project (DERP) in Sept 2021.[1] This review targeted belimumab or voclosporin compared to placebo or an active comparator. Belimumab is a B-lymphocyte stimulator (BLyS)-specific inhibitor that was originally approved in 2011 for the intravenous treatment of adults with active, autoantibody-positive SLE on standard therapy.[15] A subcutaneous version became available in 2017 and in 2020 it obtained an expanded FDA indication for the treatment of adults with active lupus nephritis on standard therapy (e.g. cyclophosphamide + azathioprine, or MMF). Voclosporin is a calcineurin-inhibitor which was approved in 2021 for treatment of adults with active lupus nephritis in combination with background immunosuppressive therapy (e.g. MMF).

The review included RCTs published through June 30, 2021 in adults with LN.[1] Two RCTs investigated belimumab compared to placebo or an active treatment and 2 RCTs evaluated voclosporin versus placebo. All trials enrolled participants with at least Class III LN, majority female participants, and included participants from the US. Three studies had moderate RoB, primarily due to extensive pharmaceutical sponsor involvement, while the AURA-LV trial of voclosporin had high RoB due to sponsor involvement and methodologic concerns including high attrition, lack of summary estimates, baseline group imbalances, and lack of blinding.[1] **Table 4** summarizes the RCTs included in the DERP report.[1]

Table 4. Inclusion Criteria of Eligible Randomized Controlled Trials[1]

Author, Year Trial Name Trial Number Locations	Patient Enrollment Inclusion/Exclusion Duration	Participant Characteristics	Treatment Arms; Enrollment	Risk of Bias
Belimumab				
Atisha-Fregoso et al., 2021 **CALIBRATE**[a] NCT02260934 US (14 sites)	• N=43 • Adults aged ≥ 18 years Lupus nephritis of class III, class IV, or class V in combination with class III or IV • No previous treatment with rituximab, belimumab, atacicept (investigational agent), or other biologic B cell therapy • 48 weeks + 48 weeks follow-up	Characteristics • Mean age, years (SD): 33.5 years (10.26) • Female sex, n of N (%): 37 of 43 (86.0%) Race/ethnicity, n (%) • Asian: 5 (11.6) • Black: 18 (41.9) • Hispanic or Latino: 15 (34.9)	• Belimumab + rituximab + CYC; N=21 • Rituximab + CYC; N=22	Moderate

		• Other/unknown: 4 (19.3) • White: 16 (37.2)		
Furie et al., 2020 **BLISS-LN** NCT01639339 US + 20 countries (107 sites)	• N=448 • Adults aged ≥ 18 years • No previous treatment with rituximab, belimumab, atacicept, or other biologic B cell therapy • No receipt of dialysis within previous 12 months • 52 weeks + 52 weeks follow-up	Characteristics • Mean age, years (SD): 33.4 years (10.7) • Female sex, n of N (%): 393 of 446 (88.1) Self-identified race or ethnicity, n (%) • American Indian or Alaska Native: 10 (2.1) • Asian: 223 (49.8) • Black: 61 (13.6) • Multiple races or ethnicities: 4 (0.9) • White: 148 (33.0)	• Belimumab + CYC-AZA; N=60 • Belimumab + MMF; N=164 • Placebo + CYC-AZA; N=59 • Placebo + MMF; N=165	Moderate
Voclosporin				
Rovin et al., 2019 **AURA-LV** NCT02141672 US + 19 countries (79 sites)	• N=265 • Adults aged ≥ 18 to 75 years • Lupus nephritis of class III, class IV, or class V in combination with class III or IV • Not receiving dialysis • Not a kidney transplant recipient • 48 weeks + up to 52 weeks follow-up	Characteristics • Mean age, years (SD): 31.7 years (10.5) • Female sex, n of N (%): 230 of 265 (86.8) Race, n (%) • Asian-Indian subcontinent: 60 (22.6) • Asian-other: 72 (27.2) • Black: 14 (5.3) • Other: 11 (4.2) • White: 108 (40.8)	• Voclosporin, low-dose (23.7 mg twice daily); N=89 • Voclosporin, high-dose (39.5 mg twice daily); N=88 • Placebo, low-dose; N=44 • Placebo, high-dose; N=44	High
Rovin et al., 2021 **AURORA 1** NCT03021499 US + 26 countries (142 sites)	• N=357 • Lupus nephritis of class III, class IV, or class V in combination with class III or IV • 52 weeks	Characteristics • Mean age, years (SD): 31.5 years (18-71) • Female sex, n of N (%): 313 of 357 (87.7) Race, n (%) • Asian: 109 (30.5) • Black: 45 (12.6)	• Voclosporin, 23.7 mg twice daily + MMF; N=179 • Placebo + MMF; N=178	Moderate

		• Other (e.g. American Indian, Alaska native, non-Black mixed race): 74 (20.7) • White: 129 (36.1) <u>Ethnicity, n (%)</u> • Hispanic or Latino: 116 (32.5) • Non-Hispanic or non-Latino: 240 (67.2) • Unknown: 1 (0.3)		
Note: [a]CALIBRATE participants had a 3-week run-in period of prednisolone and methylprednisolone before being randomized. Abbreviations: CYC=cyclophosphamide; CYC-AZA=cyclophosphamide-azathioprine; MMF=mycophenolate mofetil.				

Table 5. Trial Outcomes of Included Studies[1]

Trial Name	**Renal Response, n of n (%)**	**CRR or PERR Definition**	**Disease activity SELENA-SLEDAI, n of n (%)**
Belimumab			
CALIBRATE Belimumab (n = 21) vs. placebo (n = 22)	<u>Secondary outcomes</u> • CRR at week 48: 8 of 21 (38.0) vs. 7 of 22 (31.8); OR not reported ARR, 4.5% (95% CI, −23.4 to 32.5; *P* = 0.76) • CRR at week 96: 5 of 21 (23.8) vs. 4 of 22 (18.2); OR not reported ARR, 5.6% (95% CI -18.7 to 30.0; *P* = 0.67)	CRR: 1. UPCR < 0.5 AND 2. eGFR no worse than 20% below the pre-flare value *OR* ≥ 120 ml per minute per 1.73 m^2 AND 3. Adherence to the prednisone dosing provisions	N/A
BLISS-LN Belimumab (n = 223) vs. placebo (n = 223)	<u>Primary outcome</u> • **PERR at week 104: 96 of 223 (43.0) vs. 72 of 223 (32.3); HR, 1.46; 95% CI, 1.07 to 1.98; *P* = 0.02** **ARR, 10.8% (95% CI, 1.8 to 19.7; *P* = 0.02); NNT, 10** <u>Secondary outcome</u>	PERR : 1. UPCR ≤ 0.7 AND 2. eGFR no worse than 20% below the pre-flare value *OR* ≥ 60 ml per minute per 1.73 m^2 AND 3. No use of rescue therapy for treatment failure CRR: 1. UPCR < 0.5 AND	N/A

	• **CRR at week 104: 67 of 223 (30.0) vs. 44 of 223 (19.7); RR, 1.52; 95% CI, 1.09 to 2.12; *P* = 0.01** **ARR, 10.3% (95% CI, 2.3 to 18.3; *P* = 0.01); NNT, 10**	2. eGFR no worse than 10% below the pre-flare value *OR* ≥ 90 ml per minute per 1.73 m^2 AND 3. No use of rescue therapy	
Voclosporin			
AURA-LV Voclosporin, low-dose 23.7 mg twice daily (n = 89) vs. voclosporin, high-dose 39.5 mg twice daily (n = 88) vs. placebo (n = 88)	<u>Primary outcome, CRR at 24 weeks</u> • **Voclosporin, low-dose: 29 of 89 (32.6); RR, 1.69 (95% CI, 1.00 to 2.84; *P* = 0.046)** **ARR, 13.3% (95% CI, 0.5 to 26.0; *P* = 0.046); NNT, 8** • Voclosporin, high-dose: 24 of 88 (27.3); RR, 1.41; 95% CI, 0.82 to 2.44; *P* = 0.22 ARR, 7.9% (95% CI, −4.5 to 20.4; *P* = 0.22); • Placebo: 17 of 88 (19.3) <u>Secondary outcome, CRR at 48 weeks</u> • **Voclosporin, low-dose: 44 of 89 (49.4); RR, 2.07; 95% CI, 1.35 to 3.18; *P* < 0.001** • **ARR, 25.6% (95% CI, 11.9 to 39.3; *P* < 0.001); NNT, 4** • **Voclosporin, high-dose: 35 of 88 (39.8); RR, 1.67; 95% CI, 1.06 to 2.62; *P* = 0.02** **ARR, 15.9% (95% CI, 2.3 to 29.5; *P* = 0.02); NNT, 7** • Placebo: 21 of 88 (23.9)	CRR: 1. UPCR to ≤ 0.5 mg/mg AND 2. eGFR no worse than 20% of baseline value <u>OR</u> ≥ 60 ml/min per 1.73 m^2	<u>Score > 6 at 48 weeks,</u> n of n (%): • Voclosporin, low-dose 26 of 89 (29.2) • voclosporin, high-dose 36 of 88 (40.9) • placebo, 47 of 88 (53.4) *P* not reported
AURORA 1 Voclosporin, low-dose (n = 179) vs. placebo (n = 178)	<u>Primary outcome</u> • **CRR at 52 weeks: 73 of 179 (40.8) vs. 40 of 178 (22.5); RR, 1.81; 95% CI, 1.31 to 2.51; *P* < 0.001** **ARR, 18.3% (95% CI, 8.8 to 27.8; *P* < 0.001); NNT, 6** <u>Secondary outcome</u>	CRR: 1. UPCR to ≤ 0.5 mg/mg AND 2. eGFR no worse than 20% of baseline value <u>OR</u> ≥ 60 ml/min per 1.73 m^2	<u>Least squares mean at 24 weeks</u> • Voclosporin (n = 167): -4.5 (95% CI, -5.4 to -3.7) • placebo (n = 172): -4.1 (95% CI, -5.0, -3.2); • mean difference, -0.5 (95% CI, -1.6 to 0.6 *P* = 0.37)

	• **CRR at 24 weeks: 58 of 179 (32.4) vs. 35 of 178 (19.7); RR, 1.65; 95% CI, 1.14 to 2.37; *P* = 0.006** **ARR, 12.7% (95% CI, 3.7 to 21.7; *P* = 0.006); NNT, 8**		<u>Least squares mean at 52 weeks</u> • Voclosporin (n = 150): -6.0 (95% CI, -6.7 to -5.2) • placebo (n = 160): -5.5 (95% CI, -6.3 to -4.7); • mean difference, -0.5 (95% CI, -1.4 to 0.4; *P* = 0.28)
• **Bold** text indicates statistically significant between group differences. • ARRs, RRs, and NNTs were calculated by Drug Effectiveness Review Project. NNTs were rounded for clarity. • Abbreviations: ARR=absolute risk reduction; CI=confidence interval; CRR=complete renal response; eGFR=estimated glomerular filtration rate; HR=hazard ratio; n=number; N/A=not applicable; NNT=number needed to treat; OR=odds ratio; PERR=primary efficacy renal response; RR=risk ratio; SD=standard deviation; SELENA-SLEDAI=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment–Systematic Lupus Erythematosus Disease Activity Index; UPCR=urine protein to creatinine ratio.			

The primary or secondary outcome in all studies was CCR, although the definition of CCR varied slightly across the different RCTs (**Table 5**).[1] The phase 2 CALIBRATE study of belimumab in combination with rituximab + cyclophosphamide did not find statistically significant CCR differences at week 48 or 96 versus rituximab + cyclophosphamide alone. This study included a steroid run-in phase and was the smallest trial evaluated in the DERP report. The BLISS-LN RCT found belimumab versus placebo to be statistically significant for the primary endpoint of PERR (43.0% vs. 32.3%; HR 1.46, 95% CI 1.07 to 1.98, P = 0.02) and secondary endpoint of CRR (30.0% vs. 19.7%, RR 1.52, 95% CI 1.09 to 2.12, P = 0.01) at week 104.[1] When analyzed by concomitant induction therapy (induction therapy received prior to randomization to belimumab or placebo), those taking belimumab with MMF were more likely to achieve PERR (46.3% vs. 34.1%, OR 1.58, 95% CI 1.00 to 2.51) and CRR (34.1% vs. 20.1%, OR 2.01, 95% CI 1.19 to 3.38) than placebo at week 104.[1] Belimumab with cyclophosphamide +azathioprine were not statistically significantly different than placebo.[1] In the AURA-LV RCT, voclosporin was found to be statistically significant for the primary endpoint of CRR at 24 weeks in the low-dose group vs. placebo (32.6% vs. 19.3%; RR 1.69, 95% CI 1.00 to 2.84, P 0.046), but not the high-dose group (27.3% vs. 19.3%; RR 1.41, 95% CI 0.82 to 2.44, P 0.22).[1] At 48 weeks the CRR was statistically significant for both low-dose (49.4% vs. 23.9%; RR 2.07, 95% CI 1.35 to 3.18, P<0.001) and high-dose groups (39.8% vs. 23.9%; RR 1.67, 95% CI 1.06 to 2.62, P=0.02) when compared to placebo.[1] AURORA 1 found low-dose voclosporin to be statistically significantly better than placebo at achieving CRR at both week 52 (40.8% vs. 22.5%; RR 1.81, 95% CI 1.31 to 2.51, P<0.001) and week 24 (32.4% vs. 19.7%; RR 1.65, 95% CI 1.14 to 2.37, P=0.006).[1]

A post-hoc subgroup analysis conducted during the AURORA 1 RCT found that those receiving voclosporin were more likely to have CRR regardless of ethnicity (Hispanic or Latino vs. non-Hispanic or non-Latino).[1] Additional subgroup analyses of BLISS-LN, AURA-LV, and AURORA 1 show varying results of efficacy of the research medications versus placebo, though it is unclear what conclusions may be drawn given the smaller samples sizes provide less power to detect differences.[1]

Adverse event (AE) rates were reported differently across the 4 studies.[1] The CALIBRATE RCT reported 47 serious TEAEs; events were experienced in 19% of those in the belimumab group and 50% of those in the placebo group.[1] BLISS-LN had a more balanced severe adverse event (SAE) rate with 25% belimumab and 29.9% placebo. Four deaths from SAE were reported in the belimumab patients and 3 in patients randomized to placebo during trial intervention. A description of AEs based on induction treatment was not provided. Induction therapy was chosen by investigators up to 60 days before day 1 of trial with randomization stratified by induction treatment. Belimumab reduced the risk of renal related events (including progression to ESRD and increased proteinuria) or death in the BLISS-LN RCT (HR 0.5; 95% CI 0.3-0.8, P=0.001).[1] Discontinuations due to AEs occurred in 13% of patients in both belimumab and placebo treated groups. The

most common side effects were URTI (12% vs. 11%), UTI (7% vs. 6%), herpes zoster (6% vs. 4%), bronchitis (5% vs. 4%), nasopharyngitis (4% both groups), headache (4% vs. 2%), nausea (4% vs. 2%), and rash (3% vs. 2%).[1]

Voclosporin patients in both dosage groups of AURA-LV experienced more SAEs than placebo patients (low-dose, 25 of 89 [28.1%]; high-dose 22 of 88 [25%]; placebo 14 of 88 [15.9%]).[1] There were 12 deaths in the voclosporin groups (10 low-dose, 2 high dose), and 1 in the placebo group. Nine of these occurred in the first 2 months of the study; 7 occurred in 2 study sites in Bangladesh. The most common SAE observed with low-dose voclosporin, high-dose voclosporin, and placebo were infections and infestations (12.4% vs. 13.6% vs. 8.0%), renal and urinary disorders (5.6% vs. 1.1% vs 1.1%), nervous system disorders (4.5% vs. 3.4% vs. 1.1%), reversible posterior leukoencephalopathy syndrome PRES (2.2% vs. 2.3% vs. 0%), GI disorders (2.2% vs. 2.3% vs. 1.1%), vascular disorders (2.2% vs. 2.3% vs. 0%), and hypertension (2.2% vs. 2.3% vs. 0%).[1] In the AURORA 1 RCT, 11% of participants in the voclosporin group and 15% of participants in the placebo arm discontinued treatment early due to AE. Serious adverse effects were equal in each arm (21%). There was 1 voclosporin and 5 placebo patient deaths during the study.[1] The most common AE were infections and infestations (voclosporin 65% vs. placebo 57%), GI disorders (47% vs. 34%), investigations and infestations (34% vs. 17%), nervous system disorders (26% vs. 15%), skin and subcutaneous tissue disorders (24% vs. 17%), musculoskeletal and connective tissue disorders (22% vs. 26%), vascular disorders (21% vs. 13%), general disorders and administration site conditions (20% vs. 18%), blood and lymphatic system disorders (20% vs. 16%), respiratory, thoracic, and mediastinal disorders (15% vs. 10%), renal and urinary disorders (15% vs. 21%), and metabolism and nutritional disorders (14% vs. 21%).[1]

There is currently one ongoing study, AURORA 2, a continuation study of AURORA 1, to evaluate the long-term safety, effectiveness, and quality of life (QoL) of voclosporin compared to placebo. DERP was unable to identify any ongoing studies of belimumab which met search criteria.[1]

Cochrane-Interventions for Idiopathic Steroid-Resistant Nephrotic Syndrome in Children[16]

A 2019 Cochrane report reviewed the benefits and harms of interventions used in children 3 months to 18 years with nephrotic syndrome who do not achieve remission after a minimum of 4 weeks of GC therapy. Randomized controlled trials and quasi-randomized controlled trials were included to compare different immunosuppressants. Studies enrolling both children and adults, where the data could not be separated, were included in the analysis with all patients.[16] The reported results focus on the available comparative evidence between agents in the immunosuppressant class.

Little or no difference was found between tacrolimus and cyclosporine in the number of patients who achieve complete or partial remission (2 studies, 58 participants: RR 1.05, 95% CI 0.87 to 1.25, low certainty evidence) or in the number of patients with worsening hypertension (2 studies, 58 participants: RR 0.41, 95% CI 0.08 to 2.15, low certainty evidence).[16] There is likely little or no difference between cyclosporine compared with MMF plus dexamethasone in the number of patients who achieve complete or partial remission (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24, moderate certainty evidence), deaths (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24), or patients with 50% reduction in glomerular filtration rate (GFR) (1 study, 138 participants: RR 2.29, 95% CI 0.46 to 11.41, low certainty evidence).[16] Among those with complete remission, tacrolimus compared with MMF may increase the number who maintain complete or partial response for 12 months (1 study, 60 children: RR 2.01, 95% CI 1.32 to 3.07, low certainty evidence).[16]

Cochrane- Interventions for Renal Vasculitis in Adults[17]

A 2020 Cochrane report reviewed steroid and non-steroid medication treatments and plasma exchange in the treatment of renal vasculitis, it was an update of a previous 2008 and 2015 Cochrane review to answer questions such as dose and duration of therapy and role of new therapies. Overall, availability of direct comparative data of oral immunosuppressant (the focus of this summary) was limited by few trials and small sample sizes.[17] Risk of any relapse was statistically significantly lower for azathioprine maintenance therapy (n=76) compared to MMF (n=80) (MMF 55.3% vs. azathioprine 37.5%, RR 1.47, 95% CI 1.04 to 2.09).[17]

Comparison of major relapses and minor relapses between the two agents did not yield statistically significant results.[17] Other outcomes such as death were not reported for this comparison, and there were no statistically significant differences in any adverse event (MMF 28.9% vs. azathioprine 35%, RR 0.83, 95% CI 0.52 to 1.31).[17]

Cochrane- Belimumab for Systemic Lupus Erythematosus[18]

A 2021 Cochrane report reviewed the benefits and harms of belimumab in SLE. Six RCTs (n=2917) ranging from 84 days to 76 weeks were included in the analysis and participants were 22 to 80 years old and primarily female. Bias was low with the exception of attrition bias, which was rated as high in 67% of RCTs.[18] Background therapy varied across trials.[18] There is moderate to high-certainty evidence that more patients on belimumab compared to placebo at 52 weeks had at least a 4 point improvement on the SELENA-SLEDAI scale at the FDA approved 10 mg/kg dose (belimumab 52.2% vs. placebo 39.4%, RR 1.33, 95% CI 1.22 to 1.45, I^2=0%, high certainty evidence).[18] The change in health related quality of life assessed by the Short Form-36 Physical Component Summary Score improvement indicates there was probably little to no clinical difference between groups (mean difference 1.6 points, 95% CI 0.30 to 2.90; n=401 belimumab vs. n=400 placebo, I^2= 0%, 2 RCTs, moderate-certainty evidence).[18] More patients treated with belimumab had a GC dose reduction of greater than 50% compared to placebo (30.1% belimumab vs. 19.4% placebo, RR 1.59, 95% CI 1.17 to 2.15, I^2= 0%, 2 RCTs; high-certainty evidence).[18]

Evidence on harms was inconclusive between belimumab and placebo treatment. Those experiencing one or more serious adverse reaction was similar between groups (14% belimumab vs. 17% placebo, RR 0.87, 95% CI: 0.68 to 1.11, I^2= 48%, 5 RCTs, low-certainty evidence).[18] One or more serious infection (3.4% belimumab vs. 4.2% placebo, RR 1.01, 95% CI: 0.66 to 1.54, I^2= 0%, 4 RCTs, moderate-certainty evidence) and withdrawals due to adverse events (6.6% belimumab vs. 7.9% placebo, RR 0.82, 95% CI: 0.63 to 1.07, I^2= 0%; 5 RCTs; moderate-certainty evidence) were also similar.[18] Mortality was infrequent in both groups (9/1714 belimumab vs. 6/1203 placebo, Peto odds ratio 1.15, 95% CI 0.41 to 3.25, I^2= 4%; 6 RCTs; low-certainty evidence).[18]

Cochrane-Non-Corticosteroid Immunosuppressive Medications for Steroid-Sensitive Nephrotic Syndrome in Children[19]

A 2020 Cochrane report reviewed the benefits and harms of non-corticosteroid immunosuppressive medications in steroid-sensitive nephrotic syndrome in children who experience a relapsing course or during their first episode of nephrotic syndrome. Studies were searched through March of 2020 for RCTs and quasi-RCTs to update a previously published report. Forty-three studies (n=2428) were included.[19] Risk of relapse at 12 months was not significantly higher for MMF compared to cyclosporine (10 events vs. 7 events, RR 1.9, 95% CI 0.66 to 5.46, n=82, I^2=30.23%, low certainty evidence).[19] Gum hypertrophy and hypertrichosis were less likely with MMF compared to cyclosporine (gum hypertrophy, RR 0.09, 95% CI 0.02 to 0.47, n=144, low certainty evidence; hypertrichosis, RR 0.23, 95% CI 0.10 to 0.50, n=140, low certainty evidence).[19] There was no statistical difference in rates of hypertension, lymphopenia, or reduced GFR between cyclosporine and MMF (low certainty evidence).[19]

After review, 88 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients[20]

In 2020 guidelines for the treatment of psoriasis in pediatric patient were published. Recommendations related to oral immunosuppressant agents are limited to cyclosporine. Evidence was graded on a 3 point scale of I (good quality patient-oriented evidence), II (limited-quality patient oriented evidence) and III (Other evidence, including consensus guidelines, expert opinion, case studies, or disease-oriented evidence). Recommendations were ranked as A (based on consistent

and good quality patient oriented evidence), B (based on inconsistent or limited-quality patient oriented evidence) or C (based on consensus, expert opinion, case studies, or disease-oriented evidence.
The recommendations related to oral cyclosporine use in the treatment of pediatric psoriasis were:

- Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children. (Level of Evidence II-III, Strength of Recommendation B)
- Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children. (Level of Evidence III, Strength of Recommendation B)
- Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use. (Level of Evidence III, Strength of Recommendation C)
- Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine. (Level of Evidence III, Strength of Recommendation A)
- Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine. (Level of Evidence III, Strength of Recommendation C)

2019 Update of the European League Against Rheumatism (EULAR) Recommendations for the Management of Systemic Lupus Erythematosus[12]
In 2019, EULAR updated the previous 2008 guidelines for the treatment of SLE. The systematic literature search included publications from January 2008 to December 2017. Levels of evidence were based on the Oxford Centre and grading of recommendations used GRADE methods (**Table 6**), and task force members were asked to rate their level of agreement from 0 to 10 (full agreement being 10) with final recommendation/statements after the committee had reached consensus. Agreement was reported numerically. Recommendations with the management of SLE are summarized in **Table 7**.

Table. 6 EULAR Guidelines Levels of Evidence and Grading of Recommendations[12,21]

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (LoE)		
LoE	**Therapy/Prevention/Etiology/Harm**	**Risk factors/Prognosis**
1a	Systematic reviews of RCT	Systematic review of inception cohort studies
1b	Individual, high-quality RCT	Individual inception cohort study (high quality)
2a	Systematic reviews of cohort studies	Systematic review of retrospective cohort studies or data from RCT
2b	Cohort study or low quality RCT	Retrospective cohort study or data from RCT
2c	"Outcomes" research studies	"Outcomes" research studies

3a	Systematic review of case-control studies	
3b	Case-control studies	
4	Case-series (and poor-quality cohort and case-control studies)	Case-series (and poor-quality prognostic cohort) studies)
5	Expert opinion	Expert opinion
	Grading of recommendations, assessment, development and evaluations (GRADE)	
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies; or extrapolations from level 1 studies	
C	Level 4 studies; or extrapolations from level 2 or 3 studies	
D	Level 5 evidence; or very inconsistent or inconclusive studies of any level	

Table 7. EULAR Recommendations for Management of Systemic Lupus Erythematosus[12]

Recommendation/Statement	**Level of Agreement (SD)**
1. Goals of treatment	
1.1 Treatment in SLE should aim at remission or low disease activity (2b/B) and prevention of flares (2b/B) in all organs, maintained with the lowest possible dose of glucocorticoids.	10.0 (0)
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching or adding new therapies (2b/C).	9.95 (0.22)
2. Treatment of SLE	
2.1 HCQ	
2.1.1 HCQ is recommended for all patients with SLE (1b/A), unless contraindicated, at a dose not exceeding 5 mg/kg/real BW (3b/C).	9.65 (1.11)
2.1.2 In the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter (2b/B).	9.75 (0.70)
2.2 GC	
2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (2b/C).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (3b/C).	9.85 (0.36)

2.2.3 For chronic maintenance treatment, GC should be minimized to less than 7.5 mg/day (prednisone equivalent) (1b/B) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (2b/B).	9.90 (0.30)
2.3 Immunosuppressive therapies	
2.3.1 In patients not responding to HCQ (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, (1b/B) azathioprine (2b/C) or mycophenolate (2a/B) should be considered.	9.85 (0.48)
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease (2b/C).	9.85 (0.48)
2.3.3 Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents (2b/C).	9.90 (0.30)
2.4 Biologics	
2.4.1 In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with belimumab should be considered (1a/A).	9.20 (0.81)
2.4.2 In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, rituximab can be considered (2b/C).	9.85 (0.48)
3 Specific manifestations	
3.1 Skin disease	
3.1.1 First-line treatment of skin disease in SLE includes topical agents (GC, calcineurin inhibitors) (2b/B), antimalarials (HCQ, quinacrine) (1a/A) and/or systemic GC (4/C).	10.0 (0)
3.1.2 In non-responsive cases or cases requiring high-dose GC, methotrexate (3a/B), retinoids (4/C), dapsone (4/C) or mycophenolate (4/C) can be added.	9.85 (0.48)
3.2 Neuropsychiatric disease	
3.2.1 Attribution to SLE—as opposed to non-SLE—related neuropsychiatric manifestations, is essential and can be facilitated by neuroimaging, investigation of cerebrospinal fluid, consideration of risk factors (type and timing of the manifestation in relation to the onset of lupus, patient age, non-neurological lupus activity, presence of aPL) and exclusion of confounding factors (2b/C).	9.65 (0.85)
3.2.2 Treatment of SLE-related neuropsychiatric disease includes glucocorticoids/immunosuppressive agents for manifestations considered to reflect an inflammatory process (1b/A), and antiplatelet/anticoagulants for atherothrombotic/aPL-related manifestations (2b/C).	9.85 (0.48)
3.3 Hematological disease	
3.3.1 Acute treatment of lupus thrombocytopenia includes high-dose GC (including pulses of intravenous methylprednisolone) (4/C) and/or intravenous immunoglobulin G (4/C).	9.95 (0.22)
3.3.2 For maintenance of response, immunosuppressive/GC-sparing agents such as mycophenolate (2b/C), azathioprine (2b/C) or cyclosporine (4/C) can be used.	9.75 (0.62)

3.3.3 Refractory cases can be treated with rituximab (3a/C) or cyclophosphamide (4/C).	9.65 (0.73)
3.4 Renal disease	
3.4.1 Early recognition of signs of renal involvement and—when present—performance of a diagnostic renal biopsy are essential to ensure optimal outcomes (2b/B).	9.95 (0.22)
3.4.2 Mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (2a/B) are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	9.85 (0.36)
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (1b/A).	9.45 (0.80)
3.4.4 For maintenance therapy, mycophenolate (1a/A) or azathioprine (1a/A) should be used.	9.75 (0.62)
3.4.5 In cases with stable/improved renal function but incomplete renal response (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), repeat biopsy can distinguish chronic from active kidney lesions (4/C).	9.85 (0.48)
3.4.6 Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe nephrotic syndrome (2b/C) or incomplete renal response (4/C), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.	9.50 (0.81)
4 Comorbidities	
4.1 Antiphospholipid syndrome	
4.1.1 All patients with SLE should be screened at diagnosis for aPL (1a/A).	10.0 (0)
4.1.2 Patients with SLE with high-risk aPL profile (persistently positive medium/high titers or multiple positivity) may receive primary prophylaxis with antiplatelet agents (2a/C), especially if other atherosclerotic/thrombophilic factors are present, after balancing the bleeding hazard.	9.45 (0.80)
4.1.3 For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary antiphospholipid syndrome (1b/B).	10.0 (0)
4.2 Infectious diseases	
4.2.1 Patients with SLE should be assessed for general and disease-related risk factors for infections, such as advanced age/frailty (–/D), diabetes mellitus (–/D), renal involvement (2b/B), immunosuppressive/biological therapy (1b-2b/B-C) and use of GC (1a/A).	9.85 (0.65)
4.2.2 General preventative measures (including immunizations) and early recognition and treatment of infection/sepsis are recommended (–/D).	9.90 (0.44)
4.3 Cardiovascular disease	
4.3.1 Patients with SLE should undergo regular assessment for traditional (1b/B-C) and disease-related risk factors for cardiovascular disease, including persistently active disease (1b/B), increased disease duration (1b/A), medium/high titers of aPL (1b/A), renal involvement (1b/B) (especially, persistent proteinuria and/or GFR <60 mL/min) and chronic use of GC (1b/B).	9.85 (0.65)

4.3.2 Based on their individual cardiovascular risk profile, patients with SLE may be candidates for preventative strategies as in the general population, including low-dose aspirin (2b/D) and/or lipid-lowering agents (2b/D).	9.85 (0.48)
Abbreviations: aPL=antiphospholipid antibodies; GC=glucocorticoids; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; SD=standard deviation; SLE=systemic lupus erythematosus.	

2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis Transplant Association (EULAR/ERA-EDTA) Recommendations for the Management of Lupus Nephritis[21]

In 2019, EULAR/ERA-EDTA updated the previous 2012 guidelines for the management of lupus nephritis. The systematic literature search included publications from January 2012 to December 2018. Levels of evidence were based on the Oxford Centre and grading of recommendations used GRADE methods (**Table 6**), and task force members were asked to rate their level of agreement from 0 to 10 (full agreement being 10) with final recommendation/statements after the committee had reached consensus. Agreement was reported numerically.

Goals of treatment should be optimization (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months (2b/C), 50% by 6 months (2a/B), and a UPCR target below 500–700 mg/g by 12 months (complete clinical response)(2a/B). Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to reach complete clinical response; in such cases, prompt switches of therapy are not necessary if proteinuria is improving. (2a/C).

General recommendations include the use of immunosuppressive agents, administered in combination with glucocorticoids, in class III (A) and class IV (A/C) (±V) nephritis (2a/A). In pure class V nephritis, glucocorticoids and immunosuppression are recommended in cases of nephrotic-range proteinuria (2b/B), or when UPCR exceeds 1000 mg/g despite the optimal use of renin–angiotensin–aldosterone system blockers (5/D). Additionally for adjunctive treatment, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for all patients with UPCR > 500 mg/g or arterial hypertension (5/D). More specific recommendations for initial and subsequent drug therapy are below in **Table 8**. Strategies for refractory and adjunct therapy are available but generally have low levels of evidentiary support.

Table 8. EULAR/ERA-EDTA recommendations for Initial and Subsequent management of Lupus Nephritis[21]

Recommendation/Statement	**Level of Agreement (SD)**
Initial Treatment	
For patients with class III or IV (±V) LN, MMF (target dose: 2 to 3 g/day, or MPA at equivalent dose) (1a/A) or low-dose intravenous CYC (500 mg every 2 weeks for a total of 6 doses) (1a/A) in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.	9.84 (0.37)
Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria. (1a/B)	9.32 (0.93)
Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4 (2b/B), but high-dose intravenous CYC (0.5–0.75 g/m2 monthly for 6 months) can also be considered. (1a/B)	8.88 (1.56)

To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months. (2b/C)	9.48 (0.90)
In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose)(2a/B), in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months) (2b/C) is recommended as initial treatment due to best efficacy/toxicity ratio.	9.28 (0.96)
Alternative options for class V nephritis include intravenous CY (2b/B), or CNIs (especially TAC) in monotherapy (2b/B) or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria (1b/B).	9.28 (0.92)
HCQ should be coadministered (2a/B), at a dose not to exceed 5 mg/kg/day and adjusted for the GFR (3b/C).	9.28 (1.40)
Subsequent Treatment	
If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment (1a/A)—or azathioprine (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity (1a/A).	9.80 (0.49)
Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in complete clinical response. HCQ should be continued long-term (2b/C).	9.40 (0.75)
Continuation, switching to or addition of CNIs (especially TAC) can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks (2b/B).	9.28 (1.15)
Abbreviations: aPL=antiphospholipid antibodies; CNI=calcineurin inhibitor; CYC=cyclophosphamide; ESKD=end- stage kidney disease; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; LN=lupus nephritis; MMF=mycophenolate mofetil; MPA=mycophenolic acid; RTX=rituximab; SLE=systemic lupus erythematosus; TAC=tacrolimus; UPCR=urine protein–creatine ratio.	

<u>KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases</u>[9]

In 2021 Kidney Disease: Improving Global Outcomes (KDIGO) group published updated guidelines. Strength of recommendations were given grades of Level 1 (Strong, "we recommend") and Level 2 (Weak, "we suggest"). Quality of supporting evidence is shown as Grade A (High), Grade B (Moderate), Grade C (Low), and Grade D (Very Low).

Graded recommendations specific to treatment of lupus nephritis are:

- We recommend that patients with SLE, including those with LN, be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (1C).
- We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or mycophenolic acid analogue (1B).
- We recommend that after completion of initial therapy, patients with class III or class IV LN should be placed on mycophenolic acid analogue for maintenance (1B).

After review, 7 guidelines were excluded due to poor quality or lack of applicability to research topic.

New Formulations or Indications:

Methotrexate (Reditrex®), new formulation of SC auto injector indicated for arthritis (adults and pediatrics) and psoriasis (adults) (11/27/2019)[22]

Tacrolimus (Prograf®), expanded indication for use in combination with other immunosuppressant drugs to prevent organ rejection in adults and pediatric patients receiving lung transplantation (7/14/21)[23]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts[24,25]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Mycophenolate mofetil	Cellcept	10/22/21	Warnings and Precautions	• Addition of Acute Inflammatory Syndrome • Addition of increased risk of COVID-19 infection

Randomized Controlled Trials:
A total of 356 citations were manually reviewed from the initial literature search. After further review, 356 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Anifrolumab-fnia (SAPHNELO)

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:
Anifrolumab-fnia, a human immunoglobulin G1 kappa monoclonal antibody,[5] is a type I IFN receptor antagonist indicated for the treatment of adult patients with moderate to severe SLE, who are receiving standard therapy.[26] Approval was based on data from 3 clinical studies (MUSE, TULIP-1, and TULIP-2).[2-5]

MUSE was a multi-center, double-blind, randomized, placebo-controlled, phase 2b trial, while TULIP-1 and TULIP-2 were phase 3 trials with similar design. All trials included adult patients with SLE diagnosis based on the American College of Rheumatology (1982 revised) classification criteria, and moderate to severe disease. Patients in all 3 studies had a score of 6 points or greater on the SLEDAI-2K, organ level involvement according to a BILAG assessment, and a Physician Global Assessment (PGA) score of at least 1 on a 3 point scale where 0 indicates no disease activity and a score of 3 indicates severe disease. Patients were receiving standard therapy of 1 or multiple agents (e.g., GC, antimalarials, immunosuppressants) under specified dosage maximums and these therapies were

continued during the studies. Use of oral glucocorticoids (GC), tapering, and steroid bursts varied between MUSE and the phase 3 studies. Patients with severe active lupus nephritis or neuropsychiatric SLE were excluded, as were those at risk of opportunistic infections or certain viral illnesses (**Table 12**). MUSE included 3 treatment arms (anifrolumab-fnia 300 mg, anifrolumab-fnia 1000 mg, or placebo; each given IV every 4 weeks), TULIP-1 included 3 treatment arms (anifrolumab-fnia 300 mg, anifrolumab-fnia 150 mg, or placebo; each given IV every 4 weeks), while TULIP-2 included 2 treatment arms (anifrolumab-fnia 300 mg or placebo; each given IV every 4 weeks).[2,4,5] The 300 mg dose alone received FDA approval due to lack of efficacy seen with other doses, and will be the primary focus of this summary. Randomization in all studies was stratified by SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day prednisone or equivalent), and type I IFN gene signature (high or low). All trials lasted 52 weeks, with the MUSE primary endpoint at week 24 and a secondary endpoint at week 52.[2,4,5] The phase 3 primary endpoints were assessed at week 52. Each study included use of composite endpoints for the primary outcome (see **Table 3** for details). Additional trial specific restrictions regarding investigational products, restricted medications, and corticosteroid use and doses are included below.

The phase 2B Muse study used a primary composite endpoint of SRI-4 in addition to GC tapering at week 24 in both the total population and the Type I IFN high subgroup. Details of the composite include[5]:

- Reduction in baseline SLEDAI-2K disease activity score of ≥ 4 points
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point physician global assessment (PGA) visual analogue scale (VAS)
- No worsening in BILAG-2004 defined as ≥ 1 new A or ≥ 2 new B items compared to baseline
- No discontinuation of investigational product
- Patients who need a burst of GC need to satisfy the following:
    - No increase in dose of antimalarials or disease modifying anti-rheumatic above Day 1 levels or added new antimalarials/disease modifying anti-rheumatic between Day 1 and Day 169
    - No IV corticosteroid between Day 1 and Day 169
    - No increase in oral GC above Day 1 dose or intramuscular/intraarticular (IM/IA) injection of corticosteroid after Day 71 and up to Day 169
    - No more than one course of burst of corticosteroid between Day 1 and Day 71. One course of burst is defined as burst of oral GC above Day 1 dose (up to a maximum dose of 40 mg/day prednisone or equivalent and no increase in oral GC dose for > 14 days above Day 1 dose) or 1 IM injection of corticosteroids (≤ 160 mg methylprednisolone or equivalent) or 2 IA injections of corticosteroids
    - Reduce oral GC to < 10mg/day and ≤ Day 1 dose of prednisone or equivalent by Day 85 and maintain oral GC dose < 10mg/day and ≤ Day 1 dose until Day 169 (Note: this criterion applies to subjects with oral GC ≥ 10 mg/day at baseline)

TULIP-1 used SRI-4, without the GC tapering, as the composite primary endpoint at week 52[5]:

- Reduction from baseline of ≥ 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score
- No new organ system clinical manifestations as defined by British Isles Lupus Assessment Group (BILAG) grade
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

TULIP-2 used the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA), as a primary endpoint at week 52. BICLA is a composite of:[5]

- Reduction in severity of all baseline clinical manifestations and no worsening in other organ systems, as defined by BILAG grade
- No worsening from baseline in SLEDAI-2K score
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

The MUSE study had a statistically significant SRI-4 response with GC tapering in the anifrolumab-fnia 300 mg dose group compared to placebo for the primary endpoint at week 24 (anifrolumab-fnia 300 mg 34.3% vs. placebo 17.6%; OR 2.38, 95% CI 1.19 to 4.77; NNT 6) and secondary endpoint at week 52 (anifrolumab-fnia 300 mg 51.5% vs. placebo 25.5%; OR 3.08, 90% CI 1.86 to 5.09, P<0.001).[2] The prespecified use of the high type I IFN subpopulation at week 24 showed similar results (anifrolumab-fnia 300 mg 36.0% vs. placebo 13.2%; OR 3.55, 95% CI 1.5 to 7.32; NNT 5).[2] Statistical analyses for MUSE were conducted using a type 1 error rate of 0.1 (two-sided).[2] The FDA review included a 0.05 alpha value in its statistical calculations.[5] The TULIP-1 study failed to find statistical significance for the primary endpoint of SRI-4 response at 52 weeks at either anifrolumab-fnia dose (anifrolumab-fnia 300 mg 36.1% vs. placebo 40.2%; -4.2% difference, 95% CI -14.20 to 5.82, P=0.41).[5]

The TULIP-2 study changed the primary outcome via protocol amendment after TULIP-1 failed to find statistical significance.[4,5] TULIP-1 used BICLA as a secondary endpoint (anifrolumab-fnia 300 mg 37.2% vs. placebo 26.6%; 10.6% absolute difference, 95% CI 0.59 to 19.68).[5] The change occurred after discussion with the FDA and experts and prior to data unblinding or analysis.[5] TULIP-2 showed a statistically significant difference in BICLA response at 52 weeks (anifrolumab-fnia 300 mg 47.8% vs. placebo 31.5%; 16.3% difference, 95% CI 6.3 to 26.3, P=0.001; NNT 7).[4,5] SRI-4 response results are provided as a secondary endpoint, however "results are not multiplicity adjusted and no formal inferences can be drawn from them."[27]

Limitations of these studies include differing GC use and differing composite endpoints used for efficacy assessment, making interpretation results and applicability of results to clinical practice difficult. Lack of dose response to different doses studied, uneven attrition across studies, and conflicts of interest among authors and sponsor involvement in trial designs and interpretation further increase risk of bias. Men were underrepresented given 10:1 female to male prevalence and more likelihood that men have severe disease. Non-White representation in demographics was reasonably present in MUSE and TULIP-2, less so in TULIP-1. It is unclear how exclusion of participants with active LN or need for stable treatment prior to enrollment may have reduced enrollment of men and non-White patients who tend to experience more severe disease and health disparities in treatment of SLE.

Clinical Safety:
Safety data of anifrolumab-fnia is derived from use in moderate to severe SLE over 52 weeks, pooled from the 3 studies detailed in **Table 12**.[2-4,26] The most common adverse events were included in **Table 10**. Average age of treatment population was 41 years (age 18 to 69 years), primarily female (93%), with a racial identity of 60% White, 13% Black, and 10% Asian. Those 65 years and older represented only 3% of the trial population. Given exclusion criteria, those who are immunocompromised or who had certain viral illnesses were not represented in research studies, as well as patients with active, severe lupus nephritis or neuropsychiatric lupus, and uncontrolled diabetes with a HbA1c of >8%.[26] Pregnant women were excluded. Pregnancy in women with SLE is associated with increased risk of adverse pregnancy outcomes.

Special interest adverse events included serious infections, opportunistic infections, anaphylaxis, cancer, herpes zoster, tuberculosis, influenza, non-SLE related vasculitis, and adjudicated major cardiovascular events (**Table 9**). Serious adverse reactions included hypersensitivity, which included 1 case of anaphylactic reaction and 2 cases of angioedema in patients randomized to treatment, compared with no cases in patients randomized to placebo. Most infusion reactions

were mild to moderate. Serious infections, most commonly pneumonia, occurred in 4.8% of anifrolumab-fnia and 5.6% of placebo treated patients. Fatal infections occurred in 0.4% of patients on active treatment versus 0.2% of those on placebo. Discordant rates of herpes zoster also occurred (**Table 10**), with 2 anifrolumab-fnia patients having disseminated disease requiring hospitalization compared to none on placebo. During year 1 of a 3 year open-label extension study, 30 of 218 patients (13.8%) reported a grade 3 or higher severe AE.[26] The most frequent were bronchitis (3 patients; 1.4%), gastroenteritis (2 patients; 0.9%), pharyngitis (2 patients; 0.9%), osteonecrosis (2 patients; 0.9%), and SLE flares (2 patients; 0.9%). Infections and infestations occurred in 138 of 218 patients (63.3%) throughout the extension study. Herpes zoster infections occurred in 5% of patients, 2 of 11 were disseminated and neither serious.[28]

Table 10: Adverse reactions occurring in at least 2% of patients[2-4,26]

Adverse Reaction	**Anifrolumab-fnia (300 mg Q4 weeks at 52 weeks) %**	**Placebo %**
Upper respiratory tract infection	34	23
Bronchitis	11	5.2
Infusion-related reactions	9.4	7.1
Herpes zoster	6.1	1.3
Cough	5.0	3.2
Respiratory tract infection	3.3	1.5
Hypersensitivity	2.8	0.6

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in disease activity
2) Clinical response or remission
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) SRI-4 responder at week 24 or 52
2) BICLA responder at week 52

Table 11. Pharmacology and Pharmacokinetic Properties[26]

Parameter	
Mechanism of Action	Type 1 interferon (INF) receptor antagonist binds to subunit 1 of type 1 interferon receptor (IFNAR1) inducing internalization and reducing cell surface levels, ultimately reducing downstream signaling of inflammatory and immunological processes.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	6.23 liters (L) in typical 69.1 kg systemic lupus erythematosus patient
Elimination	Non-linear, 0.193 L/day
Half-Life	Not reported, steady state achieved at Day 85
Metabolism	IFNAR1-mediated drug clearance

Table 12. Comparative Evidence Table.[2-5,26]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Study 1 NCT01438489 MUSE FDA trial ID: CD-IA-MEDI-546-**1013** MC, R, DB, PC Phase 2b	1. Anifrolumab 300 mg IV Q4wk x 48 weeks 2. Anifrolumab 1000 mg IV Q4wk x 48 weeks 3. Placebo IV Q4wk 52 weeks duration 1:1:1 randomized Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) GC tapering encouraged but at investigator discretion, allowed post-randomization but not within 8 weeks of primary (week 24) and secondary (week 52) assessments. Two GC bursts allowed (once between weeks 1	<u>Demographics</u>: Mean age 39 years Female 93.4% White 1. 35 (35.4%) 2. 51 (49.0%) 3. 41 (40.2%) Black 1. 19 (19.2%) 2. 10 (9.6%) 3. 12 (11.8%) Asian 1. 3 (3.0%) 2. 6 (5.8%) 3. 13 (12.7%) Other 1. 38 (38.4%) 2. 36 (34.6%) 3. 36 (35.3%) Hispanic 42% GC use 1. 79 (79.8%) 2. 91 (87.5%) 3. 88 (86.3%) MTX Use 1. 19 (19.3%) 2. 25 (24.5%) 3. 16 (15.7%) <u>Key Inclusion Criteria</u>: -18 to 65 years old - ≥ 40 kg -ACR classification criteria for SLE (≥ 4 of 11 criteria) -≥ 6 points (≥ 4 in clinical components) SLE by SLEDAI-2K, excluding lupus headache or organic brain syndrome	<u>mITT</u>: 1. 99 2. 104 3. 102 <u>Attrition</u>: 1. 12 (12.1%) 2. 28 (26.9%) 3. 31 (30.4%)	<u>Primary Endpoint</u>: SRI-4 at week 24 with sustained GC reduction week 12 to 24 Whole population: 1. 34 (34.3%) 2. 30 (28.8%) 3. 18 (17.6%) 1 vs. 3 OR 2.38 (90% CI 1.33 to 4.26) P=0.014 (95% CI 1.19 to 4.77) 2 vs. 3 OR 1.94 (90% CI 1.08 to 3.49) P=0.063 (95% CI 0.96 to 4.77) Type 1 High IFN subgroup: 1. 27 (36.0%) 2. 22 (28.2%) 3. 10 (13.2%) 1 vs. 3 OR 3.55 (90% CI 1.72 to 7.32) P=0.004 (95% CI 1.5 to 8.4) 2 vs. 3 OR 2.65 (90% CI 1.27 to 5.53) P=0.029 (95% CI 1.11 to 6.36) <u>Key Secondary Endpoints</u>: SRI-4 at week 52 with sustained GC reduction week 40 to 52 1. 51 (51.5%) 2. 40 (38.5%)	16.7%/6 11.2%/9 22.8%/5 15.0%/7	<u>Any AE:</u> 1. 84 (84.8%) 2. 90 (85.7%) 3. 78 (77.2%) <u>Serious AE:</u> 1. 16 (16.2%) 2. 18 (17.1%) 3. 19 (18.8%) <u>Death:</u> 1. 0 2. 1 (1.0%) 3. 0 <u>Special interest AE:</u> 1. 10 (10.1%) 2. 15 (14.3%) 3. 12 (11.9%)	N/A	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (High) Stratified 1:1 randomization, method not described. Some unbalance in Race (White, Black, Asian), GC and MTX use between groups, and disease duration. <u>Performance Bias</u>: (Low) Training and certification provided to investigators and designated site personnel. When possible, evaluation performed by single assessor. <u>Detection Bias</u>: (Low) Training and certification provided to investigators and designated site personnel. When possible, evaluation performed by single assessor. Used Type I error rate 0.1, 2-sided while FDA review included 95% CI for 0.05 error rate. <u>Attrition Bias</u>: (High) Missing data used LOCF, withdrawal without week 20 data treated as nonresponders for responder analyses, unbalanced attrition between groups, high overall attrition. <u>Reporting Bias</u>: (Low) Prespecified outcomes reported <u>Other Bias:</u> (High) Multiple CoI among authors. Industry funded (MedImmune) and publication contingent on sponsor. **Applicability**: <u>Patient</u>: Male underrepresented given normal prevalence relative to female and risk of severe disease. Patients with severe lupus nephritis or neuropsychiatric disease were excluded. <u>Intervention</u>: Appropriate based on previous studies <u>Comparator</u>: Placebo comparison appropriate <u>Outcomes</u>: Complex composite outcomes with differing GC protocols difficult to interpret clinically <u>Setting</u>: 79 sites in 15 countries; 36.8% Latin America, 30.9% North America, 25.4% Eastern Europe, 6.8% Asia

	& 10, once between weeks 24 & 40) if needed for increased SLE disease activity	-organ domain score ≥ 1A or ≥ 2B BILAG-2004 -PGA 1 or higher on VAS -antinuclear, anti-dsDNA, or anti-Smith antibody seropositive -stable treatment with at least one: pred or equivalent, antimalarial agent, azathioprine, mycophenolate mofetil, mycophenolic acid, or MTX <u>Key Exclusion Criteria</u>: -active, severe lupus nephritis -neuropsychiatric SLE - >1 prescribed NSAID at anti-inflammatory dose within 2 weeks -Primary immunodeficiency, certain infectious diseases-HIV, active HBV, HCV, hx severe HSV, unresolved HSV within 12 weeks, any clinically significant active infection, any infection requiring hospitalization or IV anti-infectives within 60 days -cancer history (except certain squamous or basal		3. 26 (25.5%) 1 vs. 3 OR 3.08 (90% CI, 1.86 to 5.09) P<0.001 2 vs. 3 OR 1.84 (90% CI, 1.11 to 3.04) P=0.063 BICLA responder week 52 1. 53 (53.5%) 2. 42 (41.2%) 3. 26 (25.7%) 1 vs. 3 OR 3.42 (90% CI, 2.06 to 5.68) P<0.001 2 vs. 3 OR 2.06 (90% CI, 1.25 to 3.42) P=0.018				

		cell carcinomas or cervical cancer)						
2. Study 2 NCT02446912 TULIP-1 FDA trial ID: D3461C-000**05** MC, R, PC, phase 3	1. Anifrolumab 300 mg IV Q4wk x 48 weeks 2. Anifrolumab 150 mg IV Q4wk x 48 weeks 3. Placebo IV Q4wk 52 weeks duration 2:1:2 randomization Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) Patients with baseline pred ≥ 10 mg/day (or equivalent) had required taper attempt to ≤ 7.5 mg/day pred between week 8 and week 40.	<u>Demographics</u>: -Age (yr) 1. 42.0±12.0 3. 41.0±12.3 -Female 92.3% -Race White 1. 69.4% 3. 74.5% Black 1. 29 (16.1%) 3. 23 (12.5%) Asian 1. 11 (6.1%) 3. 5 (2.7%) Other 9.3% Ethnicity Hispanic/Latino NR US/Canada 40.4% <u>Key Inclusion Criteria</u>: See TULIP-2 <u>Key Exclusion Criteria</u>: See TULIP-2	<u>ITT</u>: 1. 180 2. 93 3. 184 <u>Attrition</u>: NR	<u>Primary Endpoint</u>: SRI-4 at week 52 1. 65 (36.1%) 2. 35 (37.6%) 3. 74 (40.2%) 1 vs. 3 -4.2% difference (95% CI -14.20 to 5.82) P=0.41 2 vs. 3 -2.6% difference (95% CI -14.71 to 9.60) P=0.68 <u>Secondary Endpoints</u>: BICLA response at week 52 1. 67 (37.2%) 2. 27 (29.0%) 3. 49 (26.6%) 1 vs. 3 10.1%[5] difference (95% CI 0.59 to 19.68) P NR 2 vs. 3 2.4% difference (95% CI -9.03 to 13.87) P NR	N/A 10.6/10 NS	NR	N/A	**Risk of Bias (low/high/unclear)**: *Note: Tulip-1 results have only been published as post-hoc analysis of pooled data with Tulip-2. Full study methods are not available and risk of bias cannot be fully assessed.* <u>Selection Bias</u>: See TULIP-2 <u>Performance Bias</u>: Unable to assess. Allocation concealment using blinded identical investigational product kit. <u>Detection Bias</u>: Unable to assess. Double-blind with adequate allocation concealment <u>Attrition Bias</u>: Unable to assess. Nonresponder imputation method for missing data. <u>Reporting Bias</u>: (High) Tulip-1 results only published as post-hoc analysis of pooled data with Tulip-2 outside of FDA review. Protocol available online. <u>Other Bias:</u> Unable to assess. Funded by AstraZenica **Applicability**: <u>Patient</u>: Male underrepresented given normal prevalence relative to female and risk of severe disease. Results may not be applicable to patients with mild disease and patients with severe lupus nephritis or neuropsychiatric disease were excluded. <u>Intervention</u>: unable to assess <u>Comparator</u>: placebo appropriate to evaluate efficacy, dose appropriate given phase 2b results with lack of efficacy of 1000 mg dose <u>Outcomes</u>: unable to assess <u>Setting</u>: 146 sites in 18 countries; Descending order US, Europe, Latin America, Asia-Pacific, Other
3. Study 3 NCT02446899	1. Anifrolumab 300 mg IV Q4wk x 48 weeks	<u>Demographics</u>: -Age (yr) 1. 41.1±11.5 2. 43.1±12.0	<u>mITT</u>: 1. 180 2. 182	<u>Primary Endpoint</u>: Proportion with BICLA response at week 52	16.3%/7	<u>Serious AE:</u> 1. 15 (8.3%) 2. 31 (17%)		**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (Low) Block 1:1 randomization with interactive voice/web response system,

TULIP-2 FDA trial ID: D3461C-000**04** MC, R, PC, DB, phase 3	2. Placebo IV Q4wk 52 weeks duration 1:1 randomization Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) Patients with baseline pred ≥ 10 mg/day (or equivalent) had required taper attempt to ≤ 7.5 mg/day pred between week 8 and week 40. GC doses required to be stable during final 12 wks of trial. Other treatments stable throughout whole trial period.	-Female 93.4% -Race White 59.9% Black 1. 25 (13.7%) 2. 17 (9.4%) Asian 16.6% Other 11.9% Ethnicity Hispanic/Latino 29.8% US 37.6% Key Inclusion Criteria: -18 to 70 years old -ACR classification criteria for SLE -moderate to severe SLE by SLEDAI-2K -severe dz activity ≥ 1 organ or moderate in ≥ 2 organs by BILAG-2004 -PGA 1 or higher -antinuclear, anti-dsDNA, or anti-Smith antibody seropositive -stable treatment with at least one with dose below specified thresholds: pred or equivalent, antimalarial agent, azathioprine, mizoribine (Japan only), mycophenolate mofetil, mycophenolic acid, or MTX	Attrition: 1. 15.0% 2. 28.6%	1. 86 (47.8%) 2. 57 (31.5%) Difference 16.3% (95% CI 6.3 to 26.3%) P=0.001 Secondary Endpoints: BICLA response by subpopulation at week 52 High interferon gene signature (301/362) 1. 72/150 (48.0%) 2. 46/151 (30.7%) Difference 17.3% (95% CI 6.5 to 28.2) P=0.002 Low Interferon gene signature (61/362) 1. (46.7%) 2. (35.5%) Difference 11.2% (95% CI -13.5 to 35.8) P NR Reduction in GC dose to ≤ 7.5 mg/day sustained wk 40 to 52 among baseline GC ≥ 10 mg/day (170/362) 1. 45/87 (51.5%) 2. 25/83 (30.2%) Difference 21.2% (95% CI 6.8 to 35.7) P=0.01 Reduction ≥ 50% in CLASI at week 12 1. 24/49 (49.0%) 2. 10/40 (25.0%) Difference 24.0% (95% CI 4.3 to 43.6) P=0.04	17.3%/6 N/A 21%/5 24%/5	Death: 1. 1 (0.6%) pneumonia 2. 0 (0%) Special interest AE: 1. 25 (13.9%) 2. 18 (9.9%)		multiple stratifications. Baseline characteristics balanced. Performance Bias: (Low) Allocation concealment using blinded identical investigational product kits Detection Bias: (Low) Double-blind with adequate allocation concealment. Attrition Bias: (High) LOCF used for missing data in responder analysis (nonresponder if week 48 missing), multiple imputation for intermittent missing data used in sensitivity analysis, unbalanced attrition Reporting Bias: (High) SRI-4 used as primary outcome for belimumab for SLE and in TULIP-1. Primary endpoint changed for TULIP-2 to BICLA response after failure of SRI-4 in TULIP-1 (protocol amended prior to TULIP-2 data unblinding/analysis) Other Bias: (High) Industry sponsor designed, participated in collection, analysis, and interpretation of data, and paid for professional writing assistance. Confidentiality agreements were in place between authors and AstraZeneca. **Applicability**: Patient: Male underrepresented given normal prevalence relative to female and risk of severe disease. Results may not be applicable to patients with mild disease and patients with severe lupus nephritis or neuropsychiatric disease were excluded. Intervention: Appropriate based on previous studies Comparator: placebo comparison appropriate Outcomes: Complex composite outcomes with differing GC protocols difficult to interpret clinically, outcome changed due to lack of efficacy of a different composite outcome in other research study Setting: 113 sites in 16 countries; Descending order US, Europe, Latin America, Asia-Pacific, Other

		Key Exclusion Criteria: -active, severe lupus nephritis -neuropsychiatric SLE -suicidal ideation within 6 mo or suicidal behavior within 12 mo -HbA1c >8% (diabetic subjects only) -regular use of >1 NSAID -certain infectious diseases-HIV, active HBV, HCV, hx severe HSV, unresolved HSV/CMV/EBV, opportunistic infection requiring hospitalization within 3 years -cancer history (except certain squamous or basal cell carcinomas or cervical cancer)		Reduction of ≥ 50% in swollen/tender joints at week 52 1. 34/90 (37.5%) 2. 30/71 (42.2%) Difference 4.7% (95% CI -10.6 to 20.0) P=0.55 Annualized flare rate through week 52 1. 0.64 2. 0.43 Rate Ratio 0.67 (95% CI 0.48 to 0.94) P=0.08	NS N/A			

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; anti-dsDNA = anti-double-stranded DNA; ARR = absolute risk reduction; BICLA = British Isles Lupus Assessment Group-based composite lupus assessment; BILAG-2004 = British Isles lupus assessment group 2004 index; CLASI = cutaneous lupus erythematosus disease area and severity index; CI = confidence interval; CMV = cytomegalovirus; CoI = conflict of interest; DB = double-blind; dz = disease; EBV = Epstein-Barr virus; FDA = Food and Drug Administration; GC = glucocorticoid; HbA1c = glycosylated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSV = *herpes zoster*; IV = intravenous; LOCF = last observation carried forward; MC = multi-center; mg = milligram; mITT = modified intention to treat; mo = months; MTX = methotrexate; N = number of subjects; NSAID = non-steroidal anti-inflammatory drug; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = Placebo-controlled; PGA = Physician Global Assessment; PP = per protocol; pred = prednisone; Q = every; R = randomized; SLE = Systemic Lupus Erythematosus; SLEDAI-2K = SLE disease activity index 2000; SRI = Systemic Lupus Erythematosus Responder Index; TULIP = treatment of uncontrolled lupus via the interferon pathway; US = United States; VAS = visual analogue scale; wk = week; yr = year.

References:

1. Robalino S, Harrod C. Voclosporin (Lupkynis) and belimumab (Benlysta) for active lupus nephritis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.
2. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2017;69(2):376-386.
3. Furie R, Morand EF, Askanase AD, et al. Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus.* 2021;30(8):1254-1263.
4. Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med.* 2020;382(3):211-221.
5. FDA Center for Drug Evaluation and Research. BLA 761123 Saphnelo (anifrolumab-fnia) Clinical Review. Reference ID 4864322. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761123Orig1s000MultidisciplineR.pdf Accessed: Dec 9, 2021.
6. Gergianaki I, Bortoluzzi A, Bertsias G. Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol.* 2018;32(2):188-205.
7. Fava A, Petri M. Systemic lupus erythematosus: Diagnosis and clinical management. *J Autoimmun.* 2019;96:1-13.
8. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T115873, Systemic Lupus Erythematosus (SLE); [updated 2018 Nov 30, cited 2021 Dec 9]. Available from https://www.dynamed.com/topics/dmp~AN~T115873.
9. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4S):S1-S276.
10. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2019;71(9):1400-1412.
11. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018;93(4):789-796.
12. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736-745.
13. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T913136, Management of Systemic Lupus Erythematosus (SLE) in Adults; [updated 2018 Nov 30, cited 2021 Dec 9]. Available from https://www.dynamed.com/topics/dmp~AN~T913136. .
14. Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. *Clinical and Experimental Rheumatology.* 2014;32.
15. Benlysta (belimumab). Prescribing information. GlaskoSmithKline. Research Triangle Park, NC. Dec 2020.
16. Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev.* 2019;2019(11).
17. Walters GD, Willis NS, Cooper TE, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev.* 2020;1:CD003232.
18. Singh JA, Shah NP, Mudano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev.* 2021;2:CD010668.
19. Larkins NG, Liu ID, Willis NS, Craig JC, Hodson EM. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. *Cochrane Database Syst Rev.* 2020;4:CD002290.
20. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *Journal of the American Academy of Dermatology.* 2020;82(1):161-201.
21. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis.* 2020;79(6):713-723.

22. Reditrex (methotrexate). Prescribing Information. Cumberland Pharmaceuticals, Nashville, TN. Nov 2019.
23. Prograf (tacrolimus). Prescribing Information. Astellas Pharma. Northbrook,IL. Jul 2021.
24. Cellcept (mycophenloate mofetil). FDA Letter SUPP-046. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/050722Orig1s045,%20s046;%20050723Orig1s045,%20s046;%20050758Orig1s042,%20s043;%20050759Orig1s050,%20s051ltr.pdf Accessed Dec 2021. .
25. Cellcept (mycophenloate mofetil). Prescribing Information. Genetech. South San Fransicso, CA. Oct 2021.
26. Saphnelo (anifrolumab-fnia). Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. July 2021.
27. Supplement to: Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020;382(3):211-221.
28. Chatham WW, Furie R, Saxena A, et al. Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study. *Arthritis Rheumatol.* 2021;73(5):816-825.

Appendix 1: Current Preferred Drug List

Immunosuppressants

Generic	Brand	Route	Form	PDL
azathioprine	AZASAN	ORAL	TABLET	Y
azathioprine	AZATHIOPRINE	ORAL	TABLET	Y
azathioprine	IMURAN	ORAL	TABLET	Y
cyclosporine	CYCLOSPORINE	ORAL	CAPSULE	Y
cyclosporine	SANDIMMUNE	ORAL	CAPSULE	Y
cyclosporine	SANDIMMUNE	ORAL	SOLUTION	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	ORAL	CAPSULE	Y
cyclosporine, modified	GENGRAF	ORAL	CAPSULE	Y
cyclosporine, modified	NEORAL	ORAL	CAPSULE	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	ORAL	SOLUTION	Y
cyclosporine, modified	GENGRAF	ORAL	SOLUTION	Y
cyclosporine, modified	NEORAL	ORAL	SOLUTION	Y
everolimus	EVEROLIMUS	ORAL	TABLET	Y
everolimus	ZORTRESS	ORAL	TABLET	Y
mycophenolate mofetil	CELLCEPT	ORAL	CAPSULE	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	CAPSULE	Y
mycophenolate mofetil	CELLCEPT	ORAL	SUSP RECON	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	SUSP RECON	Y
mycophenolate mofetil	CELLCEPT	ORAL	TABLET	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	TABLET	Y
mycophenolate sodium	MYCOPHENOLIC ACID	ORAL	TABLET DR	Y
mycophenolate sodium	MYFORTIC	ORAL	TABLET DR	Y
sirolimus	RAPAMUNE	ORAL	SOLUTION	Y
sirolimus	SIROLIMUS	ORAL	SOLUTION	Y
sirolimus	RAPAMUNE	ORAL	TABLET	Y
sirolimus	SIROLIMUS	ORAL	TABLET	Y
tacrolimus	ASTAGRAF XL	ORAL	CAP ER 24H	Y
tacrolimus	PROGRAF	ORAL	CAPSULE	Y
tacrolimus	TACROLIMUS	ORAL	CAPSULE	Y
tacrolimus	PROGRAF	ORAL	GRAN PACK	Y
tacrolimus	ENVARSUS XR	ORAL	TAB ER 24H	Y
anifrolumab-fnia	SAPHNELO	IV	VIAL	N
belumosudil mesylate*	REZUROCK	ORAL	TABLET	N
voclosporin	LUPKYNIS	ORAL	CAPSULE	N
Belimumab†	BENLYSTA	IV	VIAL	N

Belimumab†	BENLYSTA	IV	SYRINGE	N
Belimumab†	BENLYSTA	SC	AUTO INJCT	N

*This medication is prior authorized under the orphan drug policy and was excluded from this review.
†This medication is categorized in the Targeted Immune Modulator class

Appendix 2: Abstracts of Comparative Clinical Trials
None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Sept 16th, 2021

# ▲	Searches	Results	Type	Actions
1	Azathioprine/ae, tu [Adverse Effects, Therapeutic Use]	11769	Advanced	Display Results | More
2	Cyclosporine/ae, tu [Adverse Effects, Therapeutic Use]	16148	Advanced	Display Results | More
3	Everolimus/ae, tu [Adverse Effects, Therapeutic Use]	1277	Advanced	Display Results | More
4	Mycophenolic Acid/ae, tu [Adverse Effects, Therapeutic Use]	5556	Advanced	Display Results | More
5	Sirolimus/ae, tu [Adverse Effects, Therapeutic Use]	6450	Advanced	Display Results | More
6	Tacrolimus/ae, tu [Adverse Effects, Therapeutic Use]	9070	Advanced	Display Results | More
7	1 or 2 or 3 or 4 or 5 or 6	41522	Advanced	Display Results | More
8	limit 7 to (english language and humans)	33679	Advanced	Display Results | More
9	limit 8 to yr="2019 -Current"	2293	Advanced	Display Results | More
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	591	Advanced	Display Results | More
11	Stents/	71237	Advanced	Display Results | More
12	10 not 11	581	Advanced	Display Results | More
13	12 not eluting.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	490	Advanced	Display Results | More

1	Azathioprine/ae, tu [Adverse Effects, Therapeutic Use]	11769	Advanced	Display Results | More	
2	Cyclosporine/ae, tu [Adverse Effects, Therapeutic Use]	16148	Advanced	Display Results | More	
3	Everolimus/ae, tu [Adverse Effects, Therapeutic Use]	1277	Advanced	Display Results | More	
4	Mycophenolic Acid/ae, tu [Adverse Effects, Therapeutic Use]	5556	Advanced	Display Results | More	
5	Sirolimus/ae, tu [Adverse Effects, Therapeutic Use]	6450	Advanced	Display Results | More	
6	Tacrolimus/ae, tu [Adverse Effects, Therapeutic Use]	9070	Advanced	Display Results | More	
7	1 or 2 or 3 or 4 or 5 or 6	41522	Advanced	Display Results | More	
8	limit 7 to (english language and humans)	33679	Advanced	Display Results | More	
9	limit 8 to yr="2019 -Current"	2293	Advanced	Display Results | More	
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	591	Advanced	Display Results | More	
11	Stents/	71237	Advanced	Display Results | More	
12	10 not 11	581	Advanced	Display Results | More	
13	12 not eluting.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	490	Advanced	Display Results | More	
14	anifrolumab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	74	Advanced	Display Results | More	
15	voclosporin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	67	Advanced	Display Results | More	
16	14 or 15	135	Advanced	Display Results | More	
17	limit 16 to (english language and humans)	85	Advanced	Display Results | More	
18	limit 17 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	26	Advanced	Display Results | More	

Appendix 4: Prescribing Information Highlights

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

LUPKYNIS (voclosporin) capsules, for oral use
Initial U.S. Approval: 2021

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

Increased risk for developing serious infections and malignancies with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death. (5.1, 5.2)

----------INDICATIONS AND USAGE----------
LUPKYNIS is a calcineurin-inhibitor immunosuppressant indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). (1, 14)

Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

----------DOSAGE AND ADMINISTRATION----------
Administration:
- LUPKYNIS must be swallowed whole on an empty stomach. (2.1)
- Administer consistently as close to a 12-hour schedule as possible, and with at least 8 hours between doses. (2.1)
- If a dose is missed, instruct the patient to take it as soon as possible within 4 hours after missing the dose. Beyond the 4-hour time frame, instruct the patient to wait until the usual scheduled time to take the next regular dose. Instruct the patient not to double the next dose. (2.1)
- Instruct patients to avoid eating grapefruit or drinking grapefruit juice while taking LUPKYNIS. (2.1, 7.1)

Dosage Recommendations:
- Before initiating LUPKYNIS, establish an accurate baseline estimated glomerular filtration rate (eGFR) and check blood pressure (BP).
  - Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk; these patients may be at increased risk for acute and/or chronic nephrotoxicity. (2.2, 5.3)
  - Do not initiate LUPKYNIS in patients with baseline BP >165/105 mmHg or with hypertensive emergency. (2.2, 5.4)
- Recommended starting dose: 23.7 mg orally, twice a day. (2.3)
- Use LUPKYNIS in combination with mycophenolate mofetil (MMF) and corticosteroids. (2.3)
- Modify the LUPKYNIS dose based on eGFR (2.3, 5.3):
  - Assess eGFR every two weeks for the first month, and every four weeks thereafter.
  - If eGFR <60 mL/min/1.73 m^2 and reduced from baseline by >20% and <30%, reduce the dose by 7.9 mg twice a day. Re-assess eGFR within two weeks; if eGFR is still reduced from baseline by >20%, reduce the dose again by 7.9 mg twice a day.
  - If eGFR <60 mL/min/1.73 m^2 and reduced from baseline by ≥30%, discontinue LUPKYNIS. Re-assess eGFR within two weeks; consider re-initiating LUPKYNIS at a lower dose (7.9 mg twice a day) only if eGFR has returned to ≥80% of baseline.
  - For patients that had a decrease in dose due to eGFR, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.
- Monitor blood pressure every two weeks for the first month after initiating LUPKYNIS, and as clinically indicated thereafter. For patients with BP >165/105 mmHg or with hypertensive emergency, discontinue LUPKYNIS and initiate antihypertensive therapy. (2.3, 5.4)
- If the patient has not experienced therapeutic benefit by 24 weeks, consider discontinuation of LUPKYNIS. (2.3)
- Consider the risks and benefits of LUPKYNIS treatment beyond one year in light of the patient's treatment response and risk of worsening nephrotoxicity. (2.3, 5.3)

Dosage Adjustments:
- Patients with severe renal impairment: the recommended dose is 15.8 mg twice daily. (2.4, 8.6)
- Patients with mild and moderate hepatic impairment: the recommended dose is 15.8 mg twice daily. (2.4, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 7.9 mg (3)

----------CONTRAINDICATIONS----------
- Patients concomitantly using strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). (4)
- Known serious or severe hypersensitivity reaction to LUPKYNIS or any of its excipients. (4)

----------WARNINGS AND PRECAUTIONS----------
- Nephrotoxicity (acute and/or chronic): May occur due to LUPKYNIS or concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction. (5.3)
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions. (5.4)
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES); monitor for neurologic abnormalities; reduce dosage or discontinue LUPKYNIS. (5.5)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels. (5.6)
- QT Prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk. (5.7)
- Immunizations: Avoid live vaccines. (5.8)
- Pure Red Cell Aplasia: Consider discontinuation. (5.9)

----------ADVERSE REACTIONS----------
The most commonly reported adverse reactions (≥3%) were: glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurinia Pharmaceuticals at 1-833-672-0028 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Moderate CYP3A4 inhibitors: Reduce LUPKYNIS daily dosage to 15.8 mg in the morning and 7.9 mg in the evening. (2.5, 7.1, 12.3)
- Strong and moderate CYP3A4 inducers: Avoid co-administration. (7.1, 12.3)
- Certain P-gp substrates: Reduce dosage of certain P-gp substrates with a narrow therapeutic window when co-administered with LUPKYNIS. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, LUPKYNIS should be used at a reduced dose. (2.4, 8.6)
- Hepatic Impairment:
  - Mild and moderate hepatic impairment: Dose reduction is required.
  - Severe hepatic impairment: Avoid LUPKYNIS use. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SAPHNELO (anifrolumab-fnia) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

SAPHNELO is a type I interferon (IFN) receptor antagonist indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. (1)

Limitations of Use: The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of SAPHNELO is not recommended in these situations. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is 300 mg as an intravenous infusion over a 30-minute period every 4 weeks. For complete dilution and intravenous administration instructions see Full Prescribing Information. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/2 mL (150 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

SAPHNELO is contraindicated in patients with a history of anaphylaxis with anifrolumab-fnia. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Serious and sometimes fatal infections have occurred in patients receiving SAPHNELO. SAPHNELO increases the risk of respiratory infections and herpes zoster. Avoid initiating treatment during an active infection. Consider the individual benefit-risk if using in patients with severe or chronic infections. Consider interrupting therapy with SAPHNELO if patients develop a new infection during treatment. (5.1)
- Hypersensitivity Reactions Including Anaphylaxis: Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported. (5.2)
- Malignancy: Consider the individual benefit-risk in patients with known risk factors for malignancy prior to prescribing SAPHNELO. (5.3)
- Immunization: Avoid use of live or live-attenuated vaccines in patients receiving SAPHNELO. (5.4)
- Not Recommended for Use with Other Biologic Therapies. (5.5)

ADVERSE REACTIONS

Most common adverse drug reactions (incidence ≥5%) are nasopharyngitis, upper respiratory tract infections, bronchitis, infusion related reactions, herpes zoster and cough. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 07/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with SLE, patients with LN
Intervention	Appendix 1
Comparator	Other appendix 1 medications, placebo for new products/indications, standard of care (NSAIDS, antimalarials)
Outcomes	Renal response, disease activity scores, hospitalizations, need for dialysis, quality of life, adverse events
Timing	Not applicable
Setting	Outpatient
Abbreviations: LN= lupus nephritis; NSAIDS=non-steroidal anti-inflammatory drugs; SLE=systemic lupus erythematosus	

Belimumab (Benlysta®)

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Benlysta® (belimumab) pharmacy or 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 ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the patient diagnosed with lupus nephritis or systemic lupus erythematosus (SLE)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is belimumab dosed appropriately and with an approved formulation for patient's age as outlined in Table 1?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient currently on other targeted immune modulators~~biologic therapy or intravenous cyclophosphamide~~?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other targeted immune modulators ~~biologics or intravenous cyclophosphamide.~~	**No:** Go to # 8
8. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE or lupus nephritis?	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Does the patient have active autoantibody-positive SLE or lupus nephritis and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to # 10. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
10. ~~Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) or lupus nephritis e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?~~ Is the patient currently taking or have a contraindication to BOTH of the following: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone)	**Yes:** ~~Approve for 6 months.~~Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Approval Criteria		
11. Does the patient have lupus nephritis AND a urine protein: creatinine ratio of >500 mg/g?	**Yes:** Go to #12	**No:** Approve for 6 months
12. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on another therapeutic immune modulator ~~biologic therapy or intravenous cyclophosphamide~~? Note: Belimumab has not been studied in combination with other therapeutic immune modulators~~biologics or intravenous cyclophosphamide~~.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1: FDA approved ages

Indication	Approved formulation	
	Intravenous (IV) powder for solution	**Subcutaneous (SC) Injection**
Systemic Lupus Erythematosus (SLE)	5 years and older	18 years and older
Lupus Nephritis	18 years and older	18 years and older
IV (usual dosage): **SLE or Lupus Nephritis:** 10 mg/kg IV infusion over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter **SC** (usual dosage): **SLE**: 200 mg SC once weekly **Lupus Nephriti**s:400 mg (two 200-mg injections) SC once weekly into abdomen or thigh for 4 doses, then 200 mg SC once weekly thereafter		

P&T/DUR Review: *02/22 (SF);8/21 (DM) 2/20, 5/18*
Implementation: *TBD; 3/1/2020; 7/1/18*

Voclosporin

Goal(s):
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Voclosporin 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 this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Does the patient have Class III, Class IV, or Class V lupus nephritis AND is a baseline assessment with one of the following: • Urinary protein to creatinine ratio • eGFR	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating lupus nephritis?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient currently on cyclophosphamide? Note: Voclosporin safety and efficacy has not been established in combination with cyclophosphamide and use is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the patient currently taking or have a contraindication to ALL of the following: • Mycophenolate OR Azathioprine • Glucocorticoids (e.g. prednisone) • Hydroxychloroquine	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have proteinuria with a urine protein: creatinine ratio of >500 mg/g?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
11. Is the patient of childbearing potential?	**Yes:** Go to #12	**No:** Approve for 6 months
12. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Does the patient have an eGFR within past 60 days? Note: Should be monitored monthly per package labeling.	**Yes:** Go to #2 Record eGFR value & date _____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Has the voclosporin dose been adjusted appropriately based on baseline eGFR and current eGFR? • If eGFR <60 mL/min/1.73 m2 and reduced from baseline by >20% and <30%, reduce the dose by 7.9 mg twice a day. Reassess eGFR within two weeks; if eGFR is still reduced from baseline by >20%, reduce the dose again by 7.9 mg twice a day. • If eGFR <60 mL/min/1.73 m2 and reduced from baseline by ≥30%, discontinue LUPKYNIS. Re-assess eGFR within two weeks; consider re-initiating LUPKYNIS at a lower dose (7.9 mg twice a day) only if eGFR has returned to ≥80% of baseline. • For patients that had a decrease in dose due to eGFR, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient's lupus nephritis improved or stabilized as assessed by one of the following: • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 12 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 2/22 (SF)
Implementation: TBD

Anifrolumab-fnia

Goal(s):

- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Anifrolumab-fnia 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 ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active central nervous system lupus or severe, active lupus nephritis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient diagnosed with moderate to severe systemic lupus erythematosus (SLE)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7
7. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Does the patient have a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to # 9. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient currently taking ALL of the following or have a documented contraindication: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone) • Methotrexate OR Azathioprine OR Mycophenolate	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 2/22 (SF)
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: Oral Glucocorticoids

Date of Review: February 2022 **End Date of Literature Search:** 10/13/2021
Generic Names: See **Appendix 2** for a list of medications

Purpose for Class Review:
To identify appropriate utilization management strategies for oral glucocorticoids.

Research Questions:
1. What is the comparative efficacy and effectiveness for oral glucocorticoids used in management of anti-inflammatory and autoimmune conditions?
2. What are the comparative harms for oral glucocorticoids used in management of anti-inflammatory and autoimmune conditions?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which one oral glucocorticoid is more effective or associated with fewer adverse events?

Conclusions:
Systematic Reviews Focused on Efficacy
- There are over 100 Cochrane reviews that evaluate evidence for the safety and efficacy of oral glucocorticoids for various clinical conditions. After reviewing published literature, Cochrane reviewers determined there is low-quality or insufficient evidence for the use of oral glucocorticoids in treating the following conditions: shoulder pain,[1] periorbital and orbital cellulitis,[2] influenza,[3] acute gout,[4] tuberculosis pleurisy,[5] acute otitis media in children,[6] myasthenia gravis,[7] optic neuritis,[8] chronic inflammatory demyelinating polyradiculoneuropathy,[9] chronic rhinosinusitis,[10,11] pulmonary sarcoidosis,[12] primary biliary cirrhosis,[13] congenital adrenal hyperplasia,[14] dengue fever,[15] cancer-related pain in adults,[16] cancer-related dyspnea in adults,[17] viral myocarditis,[18] and postherpetic neuralgia.[19]
- Three Cochrane reviews concluded current evidence does not support the use of oral glucocorticoids for management of sore throat in adults and children,[20] to hasten recovery from Guillain-Barre syndrome (GBS),[21] or for management of acute sinusitis in children and adults.[22]
- Five Cochrane reviews cited moderate or high-quality evidence for the use of glucocorticoids in specific conditions including: treatment of croup in children;[23] recovery of facial motor function in patients with Bell's palsy;[24] prevention of respiratory complications in patients with cystic fibrosis;[25] promoting disability recovery in patients with relapsing-remitting multiple sclerosis (MS) experiencing acute relapse;[26] and after treatment of an acute asthmatic exacerbation.[27] In all of these reviews glucocorticoids were compared to placebo or no treatment.

Systematic Reviews Focused on Safety
- A 2019 systematic review aimed to investigate whether chronic use of oral glucocorticoids for more than 4 months would increase mortality and vertebral fracture risk in patients with stable chronic obstructive disease (COPD).[28] A meta-analysis of 5 studies (n=1,795) demonstrated that use of long-term oral

glucocorticoids increased the risk of mortality compared to placebo (risk ratio [RR], 1.63; 95% confidence interval [CI], 1.19 to 2.23; p<0.0001; I^2 = 86%).[29] A meta-analysis of 4 studies showed long-term use of oral glucocorticoids increased the rate of vertebral fractures (odds ration [OR], 2.31; 95% CI, 1.52 to 3.50; p=0.03; I^2 = 65%).[29] These results support the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommendations to not use systemic glucocorticoids in the treatment of COPD for extended, chronic use.[30]

- The primary outcome of a 2018 systematic review was to estimate the risk of different complications related to the long-term use of oral glucocorticoids in the treatment of asthma as an add-on to chronic maintenance therapy (high dose inhaled corticosteroids and other controller medications).[21] Duration of glucocorticoid therapy ranged from 3 months to 2 years in the 15 studies that met inclusion criteria. Combining unadjusted OR of adverse events among patients who were treated with glucocorticoid compared with patients who were not, there was an increased risk of peptic ulcers 2.86 (95% CI 1.39 to 5.90), hypertension 1.28 (95% CI 1.20 to 1.36), diabetes mellitus 1.30 (95% CI 1.02 to 1.64), cataracts 1.49 (95% CI 1.29 to 1.72), infections 1.68 (95% CI 1.51 to 1.87), and fractures 1.46 (95% CI 1.25 to 1.70); the risk of osteoporosis and glaucoma was not different between groups.[21] The use of oral glucocorticoids in the chronic management of asthma is associated with a higher risk of adverse effects.[21]
- A 2016 systematic review aimed to identify the most common and serious adverse drug reactions (ADRs) associated with a short course of oral glucocorticoids in children.[31] The most serious adverse effect associated with short courses of oral glucocorticoids was infection.[31] All the children returned to a normal level of endogenous cortisol secretion within 10–12 days after discontinuation of the glucocorticoids.[31] The 3 most common adverse drug effects (ADRs) were vomiting, changes in behavior and disturbed sleep.[31] Vomiting was the most common ADRs with an incidence of 5.4% and was the most frequent reason for early discontinuation of a glucocorticoid.[31]
- There is insufficient evidence to evaluate if there are subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one oral glucocorticoid is more effective or associated with fewer adverse events.

Clinical Practice Guidelines

- The 2021 Global Initiative for Asthma (GINA) recommendations suggest a short course of oral glucocorticoids may be needed in addition to inhaled glucocorticoids for severe or uncontrolled asthma exacerbations.[32] Oral glucocorticoids should only be considered for adults with poor symptom control or frequent exacerbations despite good inhaler technique and adherence with appropriate guideline-recommended treatment, and after exclusion of other contributory factors and other add-on treatments including biologics.[32]
- In 2018, the Endocrine Society published updated clinical practice guidelines for management of congenital adrenal hyperplasia (CAH).[33] Management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism.[33] During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse effects typical of longer-acting, more potent glucocorticoids, especially growth suppression.[33] Glucocorticoid maintenance therapy recommendations in fully grown patients with CAH are presented in **Table 2.**
- According to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, oral glucocorticoids have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.[30] Long-term use of oral glucocorticoids has numerous adverse effects (Level of Evidence A) with no evidence of benefits (Level of Evidence C).[30] Long-term use of oral glucocorticoids is not recommended (Level of Evidence A).[30] Duration of therapy should not be more than 5-7 days (Level of Evidence A).[30]
- In 2017 the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) collaborated to update guidance for prescribing glucocorticoids in pregnancy and breastfeeding.[34] Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy.[34]
- In 2016 the Endocrine Society formulated clinical practice guidelines for hormonal replacement in adults with hypopituitarism.[35] Hydrocortisone is recommended for glucocorticoid replacement, usually as a 15 to 20 mg total daily dose in single or divided doses. (Strong Recommendation, Moderate-Quality Evidence).[35]

- The Endocrine Society published clinical guidelines that address the diagnosis and treatment of primary adrenal insufficiency in 2016.[36] Glucocorticoid therapy is recommended in all patients with confirmed primary adrenal insufficiency (Moderate Recommendation; High-Quality Evidence).[36]

Recommendations:

- Create a new Oregon Health Plan Fee-for-Service Preferred Drug List (PDL) entitled "Oral Glucocorticoids".
- Add at least one formulation of each glucocorticoid to the PDL after review of costs in the executive session.

Background:

Glucocorticoids are synthetic analogs of natural steroid hormones secreted by the adrenal cortex under the control of the hypothalamic-pituitary-adrenal (HPA) axis.[37] They have anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.[38] The clinical effects of glucocorticoids are predominantly achieved by regulating the transcription of anti-inflammatory genes to affect the downstream production of cytokines, cell adhesion molecules and other key enzymes involved in the host inflammatory response.[38] Glucocorticoids are used as replacement therapy in adrenal insufficiency (at physiologic doses) as well as in supraphysiologic doses for the management of dermatologic, ophthalmologic, rheumatologic, pulmonary, hematologic, and gastrointestinal disorders.[38] It is estimated that 1 to 2% of the population in the United States (US) population are on chronic glucocorticoid therapy.[39]

Glucocorticoids do not have significant mineralocorticoid, androgenic, or estrogenic activity; thus the major systemic adverse effects are from suppression of the HPA axis and Cushing's syndrome.[40] Use of glucocorticoids for greater than 2 weeks results in suppression of the HPA axis, which requires tapering of glucocorticoid doses prior to discontinuation of therapy.[40] Osteoporosis, adrenal suppression, cataracts, hyperglycemia, dyslipidemia, cardiovascular disease, psychiatric disturbances and immunosuppression are among the more serious adverse effects observed with systemic glucocorticoid therapy, particularly when used at high doses for prolonged periods.[38] Glucocorticoids are classified according to duration of effect, glucocorticoid activity and mineralocorticoid potency.[38] Dosing is expressed relative to hydrocortisone and is useful in determining comparable doses.[38] **Table 1** compares properties of oral glucocorticoids.

Table 1. Oral Glucocorticoid Properties Relative to Hydrocortisone[38]

Medication	Relative Glucocorticoid Activity	Equivalent Dose	Duration of Action	Relative Mineralocorticoid Activity
Short-acting				
Hydrocortisone	1	20 mg	8-12 hours	1
Cortisone	0.8	25 mg	8-12 hours	0.8
Intermediate-acting				
Prednisone	4	5 mg	18-36 hours	0.8
Prednisolone	4	5 mg	18-36 hours	0.8
Methylprednisolone	5	4 mg	18-36 hours	0.5
Long-acting				
Dexamethasone	30	0.75 mg	36-72 hours	0
Abbreviations: mg = milligrams				

Concomitant use of other medications should also be assessed before initiating glucocorticoid therapy as significant drug interactions have been noted with oral contraceptives, antiepileptic drugs, anticoagulants, antifungals, antibiotics, and antivirals.[38] Systemic glucocorticoids are eliminated primarily by hepatic CYP3A4 metabolism, and inhibition of the catalytic activity of CYP3A4 by other drugs can affect their elimination.[37] The drug-drug interactions mediated through CYP3A4 result either from induction (leading to a decrease in glucocorticoid availability) or from inhibition (leading to an increase in glucocorticoid availability) of this enzyme.[37]

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation 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 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.

SYSTEMATIC REVIEWS:
Efficacy of Oral Glucocorticoids
There are over 100 Cochrane reviews which evaluate the safety and efficacy of glucocorticoids for various clinical conditions. After reviewing published literature, Cochrane reviewers determined there is low-quality or insufficient evidence for the use of oral glucocorticoids in treating the following conditions: shoulder pain,[1] periorbital and orbital cellulitis,[2] influenza,[3] acute gout,[4] tuberculosis pleurisy,[5] acute otitis media in children,[6] myasthenia gravis,[7] optic neuritis,[8] chronic inflammatory demyelinating polyradiculoneuropathy,[9] chronic rhinosinusitis,[10,11] pulmonary sarcoidosis,[12] primary biliary cirrhosis,[13] congenital adrenal hyperplasia,[14] dengue fever,[15] cancer-related pain in adults,[16] cancer-related dyspnea in adults,[17] viral myocarditis,[18] and postherpetic neuralgia.[19] This class update will focus on publications that evaluate outpatient utilization of oral glucocorticoids. Three Cochrane reviews concluded current evidence does not support the use of oral glucocorticoids for management of sore throat in adults and children,[20] to hasten recovery from Guillain-Barre syndrome (GBS),[21] or for management of acute sinusitis in children and adults.[22] Five Cochrane reviews cited moderate or high-quality evidence for the use of glucocorticoids in specific conditions including: treatment of croup in children;[23] recovery of facial motor function in patients with Bell's palsy;[24] prevention of respiratory complications in patients with cystic fibrosis;[25] promoting disability recovery in patients with relapsing-remitting multiple sclerosis (MS) experiencing acute relapse;[26] and after treatment of an acute asthmatic exacerbation.[27] In all of these reviews glucocorticoids were compared to placebo or no treatment. Cochrane reviews citing moderate or high-quality evidence for the avoidance or utilization of glucocorticoids in specific conditions are summarized below.

Evidence Does Not Support Use in Specified Indication

Sore Throat

The objective of a 2020 Cochrane update was to assess the clinical benefit and safety of glucocorticoids in reducing the symptoms of sore throat in adults and children.[20] Randomized controlled trials that compared glucocorticoids to placebo or standard clinical management were included.[20] Nine trials involving 1319 participants (369 children, aged over 3 years and 950 adults) met inclusion criteria.[20] Trials were conducted in general practice or emergency department settings. Primary outcomes included: complete resolution of pain at 24 and 48 hours; mean time to onset of pain relief; and mean time to complete resolution of pain.[20] Secondary outcomes included adverse events, relapse rates and days missed from school or work.[20] Antibiotics were administered to both glucocorticoid and placebo group participants in all of the included trials.[20] Six trials used a single oral dose either dexamethasone (up to 10 mg) or prednisone 60 mg.[20] The other trials used a single intramuscular (IM) dose of betamethasone 8 mg or a combination of oral and IM glucocorticoid doses.[20] The included studies were assessed as moderate quality, but the small number of studies has the potential to increase the uncertainty, particularly if applying these results to children.[20]

Five trials reported resolution of pain at 24 hours and 4 RCTs reported pain resolution at 48 hours. In addition to any effect of antibiotics and analgesia, glucocorticoids increased the likelihood of complete resolution of pain at 24 hours compared to placebo (RR 2.4, 95% CI 1.29 to 4.47; p=0.006; I^2 = 67%; high-certainty evidence).[20] The number-needed-to-treat for an additional beneficial outcome (NNTB) was 4.8 (95% CI 2.85 to 14.28).[20] Similar results on pain resolution were observed at 48 hours (RR 1.50, 95% CI 1.27 to 1.76; p<0.001; I^2 = 0%; high-certainty evidence).[20] The NNTB at 48 hours was 4.1 (95% CI 2.4 to 16.7).[20] In a pooled analysis of 7 trials, the mean time to onset of pain relief was 6 hours earlier in participants taking glucocorticoids compared to placebo (MD −5.96, 95% CI −8.75 to −3.17; p<0.001; I^2 = 69%; moderate-certainty evidence).[20] The mean time to complete pain resolution with glucocorticoids was reduced by 21 hours compared to placebo (MD −21.01, 95% CI −26.42 to −15.61; p<0.001; I^2 = 9%; moderate-certainty evidence).[20] No differences were reported in relapse rates, days missed from work or school, or adverse events for participants taking glucocorticoids versus placebo.[20] However, the reporting of adverse events was poor, and only two trials included children or reported days missed from work or school.

In summary, a single dose of oral or intramuscular glucocorticoids, in addition to antibiotics, moderately increased the likelihood of both resolution and improvement of pain in participants with sore throat with an average difference of 6 hours in time to onset of pain relief compared to placebo.[20] Given the limited benefit, further research into the harms and benefits of short courses of steroids is needed to permit informed decision-making.[20]

Guillain-Barre Syndrome

A 2016 Cochrane review examined the ability of glucocorticoids to hasten recovery and reduce the long-term morbidity from Guillain-Barre syndrome (GBS).[41] Literature was searched through January 12 2016. Studies that evaluated of any form of glucocorticoid or adrenocorticotrophic hormone (ACTH) versus placebo or supportive care alone in GBS were included.[41] Eight RCTs with 653 participants met inclusion criteria.[41] The primary outcome of interest was change in disability grade on a 7-point scale after 4 weeks.[41] Secondary outcomes of interest included time from randomization until recovery of unaided walking, time from randomization until discontinuation of ventilation (for those ventilated), death, death or disability (inability to walk without aid) after 12 months, relapse, and adverse events.[41]

Six trials with 587 participants provided data for the primary outcome.[41] The first trial compared intramuscular ACTH daily for 10 days with placebo.[41] Four trials with between 14 and 46 participants compared oral prednisolone versus placebo, or supportive treatment without glucocorticoids and no placebo.[41] The oral regimens varied but all consisted of the equivalent of prednisolone 40 mg daily for at least 2 weeks.[41] A trial with alternate allocation included 10 participants treated with methylprednisolone 1500 mg daily for five days and 10 participants who received supportive care.[41] A trial with 242 participants compared intravenous methylprednisolone 500 mg daily for five days with an identical placebo.[41] This trial did not show a difference in any outcome assessed between

glucocorticoid and placebo groups.[41] One trial with 225 participants differed from the others in that all participants received intravenous immunoglobulin 0.4 g/kg daily for 5 days in accordance with current practice and were randomly allocated to receive intravenous methylprednisolone 500 mg daily for 5 days, or an identical placebo.[41] In this trial, the authors reported a one disability grade improvement after 4 weeks in 63 of 113 (56%) of control- and 76 of 112 (68%) methylprednisolone-treated participants (RR 1.2, 95% CI 1.0 to 1.5, p=0.06).[41] The trials could not demonstrate a difference in other outcomes between the groups, including the proportion of participants requiring ventilation, becoming able to walk unaided, and improving by 1 or more disability grades during the first year.[41]

According to moderate quality evidence, the change in disability grade after 4 weeks in the glucocorticoid groups was not different from that in the control groups (MD 0.36; 95% CI 0.16 to 0.88).[41] In 4 trials (n=120) of oral glucocorticoids, there was very low quality evidence of less improvement after 4 weeks with glucocorticoids than without glucocorticoids (MD 0.82; 95% CI 0.17 to 1.47).[41] In 2 trials (n=467), there was moderate quality evidence of no difference of disability improvement after 4 weeks with intravenous glucocorticoids (MD 0.17, 95% CI -0.06 to 0.39).[41] According to moderate quality evidence, there was also no difference between the glucocorticoid treated and control groups for improvement by 1 or more grades after 4 weeks (RR 1.08, 95% CI 0.93 to 1.24) or for death or disability after 1 year (RR 1.51, 95% CI 0.91 to 2.5).[41] High quality evidence showed the occurrence of diabetes was more common (RR 2.21, 95% CI 1.19 to 4.12) and hypertension less common (RR 0.15, 95% CI 0.05 to 0.41) in the participants treated with glucocorticoids.[41]

Based on moderate quality evidence, glucocorticoids given alone do not significantly hasten recovery from GBS or affect long-term outcomes.[41] Based on very low quality evidence, oral glucocorticoids may even delay recovery.[41] Diabetes requiring management with insulin was more common and hypertension less common with glucocorticoids based on high quality evidence.[41]

Acute Sinusitis

The objective of a 2014 Cochrane update was to assess the safety and efficacy of systemic glucocorticoids on clinical response rates in children and adults with acute sinusitis.[22] Acute sinusitis was defined by clinical diagnosis alone, or confirmed by additional radiological or nasal endoscopic examination.[22] Literature was searched for RCTs that compared systemic glucocorticoids to placebo or standard clinical care through February 2014.[22] Five RCTs (n= 1,193 adults) met inclusion criteria.[22] None of the trials included children. Three French trials performed in ear, nose and throat (ENT) outpatient clinics also used radiological assessment as part of their inclusion criteria.[22] The other 2 RCTs were conducted in primary care settings located in South Africa and the Netherlands. The primary outcome of interest was the proportion of participants with resolution or improvement of any patient-related symptoms, including total change in clinical status, measured at two time points: short-term (2 weeks or less) or long-term (more than 2 weeks).[22] All participants were assigned to either oral glucocorticoids (prednisone 24 mg to 80 mg daily or betamethasone 1 mg daily) or the control treatment (placebo in 4 trials and non-steroidal anti-inflammatory drugs in 1 trial).[22] In 4 trials antibiotics were prescribed in addition to oral glucocorticoids or control treatment, while 1 trial investigated the effects of oral glucocorticoids as a monotherapy.[22] Methodological quality was judged as moderate in 4 trials and high in 1 trial.[22]

When combining data from the 4 placebo-controlled trials, participants treated with oral glucocorticoids and antibiotics were slightly more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment at days 3 to 7 (RR 1.2, 95% CI 1.1 to 1.3; $I^2 = 0\%$; absolute risk difference [RD] 11%; 95% CI 4% to 17%) and at days 4 to 14 (RR 1.1, 95% CI 1.0 to 1.2; $I^2 = 30\%$; RD 8%, 95% CI 2% to 13%).[22] Only one high-quality trial reported on the long-term effects (more than 2 weeks) of oral glucocorticoids.[22] At 8 weeks, the proportions of patients with resolution of facial pain/pressure and total symptoms were higher in the placebo group than in the oral glucocorticoid monotherapy group, although the differences were not found to be different (RD -2.2%, 95% CI -12.6% to 8.1% and RD -9.9%, 95% CI -24.7% to 4.9%, respectively).[22] Neither of the groups differed significantly in the proportion of patients who received prescriptions for antibiotics (17/88 vs. 16/86) or intranasal glucocorticoids (6/88 vs. 15/86).[22] No trial reported effects on relapse or recurrence rates.[22]

Reported adverse effects in patients treated with oral glucocorticoids were mild (nausea, vomiting, gastric complaints) and did not significantly differ from those receiving placebo.[22]

Oral glucocorticoids as monotherapy appear to be ineffective for adult patients with acute sinusitis.[22] Oral glucocorticoids in combination with antibiotics may be modestly beneficial for short-term relief (< 14 days) of symptoms from acute sinusitis.[22] Until high-quality trials demonstrate oral glucocorticoids to be beneficial in patients with acute sinusitis, their use is not supported by current evidence.[22]

Evidence Supports Use in Specified Indication

Croup in Children

A 2018 Cochrane review examined the effects of glucocorticoids in the treatment of croup in children aged 0 to 18 years.[23] This was an update of a Cochrane Review published in 1999 and previously updated in 2004 and 2011.[23] Literature was searched through April 3, 2018.[23] Randomized controlled trials which investigated children aged 0 to 18 years with croup and measured the effects of glucocorticoids, alone or in combination, compared to placebo or another pharmacologic treatment were included.[23] For inclusion in the systematic review the studies needed to report at least 1 of the following outcomes: change in croup score from baseline; return visits or admissions or both; length of stay; patient improvement; use of additional treatments; and adverse events.[23] Five new RCTs with 330 children met inclusion criteria. This review now includes 43 RCTs with a total of 4,565 children.[23] Dexamethasone and budesonide were the most widely studied glucocorticoids in this population.[23] Most (98%) studies were assessed as having a high or unclear risk of bias due to issues with study methods, reporting or both.[23]

Compared to placebo, glucocorticoids improved symptoms of croup at 2 hours (standardized mean difference [SMD] -0.65; 95% CI-1.13 to -0.18; 7 RCTs; 426 children; moderate-certainty evidence), and the effect lasted for at least 24 hours (SMD -0.86; 95% CI -1.40 to -0.31; 8 RCTs; 351 children; low-certainty evidence).[23] Compared to placebo, glucocorticoids reduced the rate of return visits, admissions or both (RR 0.52; 95% CI 0.36 to 0.75; 10 RCTs; 1679 children; moderate-certainty evidence).[23] Glucocorticoid treatment reduced the length of stay in hospital by about 15 hours (mean difference [MD} -14.90; 95% CI -23.58 to -6.22; 8 RCTs; 476 children; quality of evidence not reported).[23] Serious adverse events were infrequent.[23] Uncertainty remains with regard to the optimal type, dose, and mode of administration of glucocorticoids for reducing croup symptoms in children.[23] In summary, glucocorticoids reduced symptoms of croup at 2 hours, shortened hospital stays, and reduced the rate of return visits to care.[23] Previous version of this review reported that glucocorticoids reduced symptoms of croup within 6 hours.[23]

Bell's Palsy

A 2016 Cochrane update evaluated the effectiveness and safety of glucocorticoid therapy in people with Bell's palsy.[24] This was an update of a review first published in 2002 and updated in 2010.[24] Literature was searched through March 2016.[24] Seven trials, including 895 participants with one-sided mild, moderate or severe Bell’s palsy met inclusion critiera.[24] Participants ranged in age from 2 to 84 years.[24] They were treated with a short course of glucocorticoids or placebo, either alone or in combination with other therapies (e.g., antivirals).[24] Glucocorticoids used in the RCTs included prednisone, cortisone, methylprednisolone, and prednisolone. One trial only involved children, from 24 months to 74 months old.[24] The duration of follow-up for the included studies from 157 days to 12 months.[24] The primary outcome of interest was incomplete recovery of facial motor function 6 months or more after randomization.[24]

Moderate- to high-quality evidence showed short-term use of glucocorticoids reduced the number of people left with facial weakness after Bell's palsy compared to placebo.[24] Overall, 79/452 (17%) participants allocated to glucocorticoids had incomplete recovery of facial motor function 6 months or more after randomization; which was fewer than the 125/447 (28%) participants in the control group (RR 0.63, 95% CI 0.50 to 0.80, 7 RCTs, n=895).[24] The number of people

who need to be treated with glucocorticoids to avoid one incomplete recovery at 6 months was 10 (95% CI 6 to 20).[24] The reduction in the proportion of participants with cosmetically disabling sequelae 6 months after randomization was very similar in the glucocorticoid and placebo groups (RR 0.96, 95% CI 0.40 to 2.29, 2 trials, n=75, low-quality evidence).[24] However, there was a reduction in motor synkinesis (i.e., crocodile tears) during follow-up in participants receiving glucocorticoids (RR 0.64, 95% CI 0.45 to 0.91, 3 trials, n=485, moderate-quality evidence).[24]

Three studies explicitly recorded adverse effects attributable to glucocorticoids.[24] One trial reported that 3 participants receiving prednisolone had temporary sleep disturbances and 2 trials gave a detailed account of adverse effects occurring in 93 participants, all non-serious.[24] The combined analysis of data from these 3 trials could not find a difference in adverse effect rates between people receiving glucocorticoids and people receiving placebo (RR 1.04, 95% CI 0.71 to 1.51, n=715).[24] Glucocorticoid courses in Bell's palsy are short and the dosed are quickly tapered, making the likelihood of adverse effects in practical use less than in longer-term indications.[24] The available moderate- to high-quality evidence from 7 RCTs showed benefit from treating Bell's palsy with glucocorticoids.[24]

Long-Term Use In Cystic Fibrosis

A 2015 Cochrane systematic review updated a previous review that assessed the effectiveness of long-term use (over 30 days) of oral glucocorticoids in respiratory complications in patients with cystic fibrosis.[25] Literature was searched through August 28, 2015.[25] Primary outcomes of interest included: improved pulmonary function tests from baseline (i.e., forced expiratory volume at 1 second [FEV_1]and forced vital capacity [FVC]), and adverse events.[25] Three studies including 354 participants met inclusion criteria.[25] The ages of the participants ranged from 1 year to 19.5 years.[25] In each study oral glucocorticoids were compared with placebo.[25] The dose of prednisolone included 1mg/kg day on alternate days, 2 mg/kg on alternate days, and 2 mg/kg daily for 14 days followed by 1 mg/kg on alternate days for 10 weeks.[25] The duration of administration of oral glucocorticoids and follow-up ranged from 12 weeks in 1 RCT to 4 years in the other 2 RCTs.[25] Common outcomes were examined at different time-points and presented differently, so meta-analyses were not possible.[25] Of the 3 studies included in this review, only one was assessed to be of moderate quality.[25] Information to fully assess the quality of the other two studies was not available.[25]

All studies showed some improvement or delay in decline in lung function in the oral glucocorticoid-treated groups compared with placebo.[25] In one RCT, the mean absolute change in percent predicted FEV_1 at 14 days was 7.7% in the treatment group compared to -1.0% in the placebo group (95% CI, 15.08 to 2.32 for difference between groups) and at 12 weeks was 6.3% in the prednisolone group compared to -1.8% in the placebo group (95% CI, 15.75 to 0.45).[25] A second RCT reported that at 4 years the mean percent-predicted FEV_1 was higher in the prednisolone group at a dose of 2 mg/kg on alternate days (103%) compared to the placebo group (87%), ($p<0.005$).[25] An excess of adverse events resulted in premature discontinuation of high dose prednisolone (2 mg/kg on alternate days).[25] When the 3 groups were compared for the initial 24 months, the mean change in percent-predicted FVC was higher in the 1 mg/kg group than the placebo group at all 6 month time points ($p<0.0001$); and at all time points the mean change in percent predicted FVC was greater in the 2 mg/kg group than the placebo group ($p<0.01$).[25] When the 1 mg/kg prednisolone group and the placebo group were compared for the first 48 months of the study, the glucocorticoid-treated group had a greater change in percent-predicted FVC, which was sustained throughout the time period ($p<0.0025$).[25] At 24 months, 70.4% participants treated with 1 mg/kg prednisolone had an increase in percent predicted FVC, compared with 54.9% participants treated with 2 mg/kg prednisolone and 41.6% participants treated with placebo.[25]

Each study reported different adverse events. One RCT specifically sought to assess adverse events including elevated blood pressure, fluid retention, and serum sodium, potassium, and glucose abnormalities.[25] The second study regularly measured height and weight of participants, but other adverse effects were not recorded.[25] The third study monitored adverse events at each clinic visit, specifically serum glucose levels, presence of cataracts, liver enzyme abnormalities, or chest infections.[25] The development of a Cushingoid appearance was reported in one study and occurred in 4 of the prednisolone-treated participants (2 mg/kg on alternate days).[25] Development of cataracts was reported in 2 studies. Data from one RCT showed that during the first 24 months, cataracts were seen more often in participants in the 2 mg/kg prednisolone group (11 participants) compared to the 1 mg/kg group (3 participants).[25] Of note, 7 participants in the placebo

group developed cataracts in this RCT.[25] Osteoporosis was not specifically noted, but in the follow-up of one trial, 2 of the prednisolone-treated participants (2mg/kg on alternate days) developed multiple bone fractures.[25] All 3 RCTs noted varying degrees of glucose intolerance.[25]

In summary, oral glucocorticoids at prednisolone-equivalent dose of 1 to 2 mg/kg on alternate days appear to slow progression of lung disease in patients with cystic fibrosis; however, benefit should be weighed against occurrence of adverse events.[25] Current evidence suggests that oral glucocorticoids at a prednisolone equivalent dose of 2 mg/kg on alternate days is effective, but should not be used long term, due to the high risk of adverse effects.[25] A dose of 1 mg/kg on alternate days may be considered for up to 24 months, but close attention to the occurrence of adverse effects (glucose abnormalities, cataracts and growth retardation) is warranted.[25]

Oral Versus Intravenous Glucocorticoids for Acute Multiple Sclerosis Relapses

The primary objective of a 2012 Cochrane Review was to compare the safety and efficacy of oral versus intravenous glucocorticoids in promoting disability recovery after acute relapses in patients with relapsing-remitting MS.[26] Literature was searched through January 2012.[26] A total of 5 studies comprising 215 participants were identified.[26] In 4 RCTs, intravenous methylprednisolone was compared with oral methylprednisolone, and in 1 RCT the oral comparator was prednisone.[26] All trials were performed in the outpatient setting of a hospital-based MS care centers in the United Kingdom (UK), Italy, Canada and Spain.[26] Three RCTs had methodological limitations with respect to randomization, concealment of allocation, and incomplete followup.[26] Two trials were of moderate or high quality.

Only one endpoint, the proportion of patients with Expanded Disability Status Scale (EDSS) improvement at 4 weeks, was common to 3 trials.[26] The pooled analysis of 3 RCTs (n=165) resulted in a mean difference change in EDSS between groups at 4 weeks of -0.22 (95% CI -0.71 to 0.26; p=0.20).[26] Four RCTs (n=200) reported the proportion of patients experiencing improvement in EDSS and relapse recovery after steroid treatment.[26] The odds ratio of improvement with oral methylprednisolone versus intravenous methylprednisolone was 0.60 (95% CI 0.28 to 1.26).[26] Analysis of the 5 trials that compared intravenous versus oral glucocorticoid therapy for MS relapses do not demonstrate any differences in clinical outcomes or adverse events.[26] Based on this evidence, oral glucocorticoid therapy may be a practical and effective alternative to intravenous steroid therapy in this population.[26] However, only 2 of the 5 studies employed rigorous methodological techniques, so these results should be interpreted with some caution.[26]

Preventing Relapse Following Acute Exacerbations Of Asthma

A 2007 review evaluated the benefit of oral glucocorticoids for the treatment of patients with asthma discharged from an acute care setting (usually the emergency department) after treatment of an acute asthmatic exacerbation.[27] Six RCTs involving 374 children and adults met inclusion criteria.[27] Oral glucocorticoids (prednisone, methylprednisolone, and dexamethasone) were provided for 7 to 10 days, usually as a tapering dose.[27] The primary outcome was relapse to additional care, defined as a patient's perceived need for further assessment and treatment within the follow-up period.[27] Overall, the methodological quality of the studies was rated as high.[27] All 6 RCTs were double-blinded, placebo controlled, and demonstrated appropriate concealment of allocation.[27]

The meta-analysis showed fewer patients in the oral glucocorticoid group received additional care in the first 7 to 10 days following discharge compared with placebo-treated patients (RR 0.38, 95% CI 0.20 to 0.74).[27] This favorable effect was maintained over the first 21 days (RR 0.47, 95% CI 0.25 to 0.89) and there were fewer subsequent hospitalizations (RR 0.35, 95% CI 0.13 to 0.95).[27] Patients receiving glucocorticoids had less need for beta2-agonists (mean difference (MD) -3.3 activations/day, 95% CI -5.6 to -1.0). Differences in changes pulmonary function tests (SMD 0.045, 95% CI -0.47 to 0.56) and adverse effects (SMD 0.03, 95% CI -0.38 to 0.44) were not found between the groups.[27] No data were reported about the specific adverse effects associated with short courses of oral glucocorticoids.[27] From these results, as few as 10 patients need to be treated to prevent relapse to additional care after an exacerbation of asthma.[27]

Safety of Oral Glucocorticoids

Long-Term Oral Glucocorticoid Use In Patients With Chronic Obstructive Pulmonary Disease

A 2019 systematic review aimed to investigate whether chronic use of oral glucocorticoids for more than 4 months increases mortality and vertebral fracture risk in patients with stable COPD.[28] Literature was searched through November 2018.[29] Five studies met inclusion criteria for a mortality meta-analysis and 4 studies (n=17,764) were pooled for an analysis of the impact of long term glucocorticoid use on vertebral fracture.[29] Among the 5 studies assessing mortality, 4 were prospective cohort studies and one was a prospective case–control study.[29] The 4 studies assessing vertebral fracture were retrospective case–control studies.[29] No RCTs were identified, and the number of included observational studies was small.[29]

A meta-analysis of 5 studies (n=1,795) demonstrated that long-term use of oral glucocorticoids increased risk of mortality compared to placebo (RR, 1.63; 95% CI, 1.19 to 2.23; p<0.0001; I^2 = 86%).[29] In the 4 studies investigating vertebral fracture, 2,048 patients were on long-term oral glucocorticoids and 15,716 patients were in the placebo groups.[29] A meta-analysis of 4 studies showed that patients long-term use of oral glucocorticoids increased rate of vertebral fractures (OR, 2.31; 95% CI, 1.52 to 3.50; p=0.03; I^2 = 65%).[29]

Adverse Events Associated With Oral Glucocorticoids In Asthma

The primary outcome of a 2018 systematic review was to estimate the risk of different complications related to the use of long-term use of oral glucocorticoids in the treatment of asthma when used as add-on to chronic maintenance therapy (high dose inhaled corticosteroids and other controller medications).[21] Literature was searched through May 2017.[21] Fifteen studies met inclusion criteria. Of the 15 studies, 11 had a cohort design, 2 were cross-sectional studies, and 2 were case-control studies.[21] Duration of glucocorticoid therapy ranged from 3 months to 2 years in the various studies. Nine studies were performed in the United States, 5 in the UK, and 1 in South Africa.[21]

Combining unadjusted OR of adverse events among patients with glucocorticoid-use compared with non-glucocorticoid use from studies, there was an increased risk of peptic ulcers 2.86 (95% CI 1.39 to 5.90), hypertension 1.28 (95% CI 1.20 to 1.36), diabetes mellitus 1.30 (95% CI 1.02 to 1.64), cataracts 1.49 (95% CI 1.29 to 1.72), infections 1.68 (95% CI 1.51 to 1.87), fractures 1.46 (95% CI 1.25 to 1.70); the risk of osteoporosis and glaucoma was not different between groups.[21] The risk of any complication increased with higher doses of glucocorticoid, with pooled adjusted OR from 2 studies of 2.26 (95% CI 1.37 to 3.72), 2.94 (95% CI 2.62 to 3.29), and 3.35 (95% CI 2.94 to 3.82) for low dose (< 5 mg), medium dose (5–10 mg) and high dose (>10 mg), respectively, (compared with no glucocorticoid use).[21] The pooled adjusted OR from 2 studies that reported the relevant adverse events among high-dose glucocorticoid-users (>10 mg) compared with non-glucocorticoid users were as follows: for the development of any complications 3.35 (95% CI 2.94 to 3.82), infections 2.68 (95% CI 2.46 to 2.91), gastrointestinal complications 2.06 (95% CI 1.96 to 2.17), psychiatric complications 1.66 (95% CI 1.55 to 1.78), cardiovascular complications 1.82 (95% CI 1.67 to 1.98), metabolic complications 1.41 (95% CI 1.32 to 1.50), bone and muscle complications 2.30 (95% CI 2.18 to 2.42), and ocular complications 1.40 (95% CI 1.31 to 1.49).[21] The use of oral glucocorticoids in the management of asthma is associated with a higher risk of adverse effects.[21] This risk is higher as the oral glucocorticoid dose increases.[21]

Short-Course Oral Glucocorticoids In Children

A 2016 systematic review aimed to identify the most common and serious ADRs associated with short-course oral glucocorticoids in children.[31] Literature was searched up to December 2013.[31] Inclusion criteria were original research studies assessing glucocorticoid toxicity in children from 28 days up to 18 years of age.[31] Thirty-eight publications met inclusion criteria. Twenty-two RCTs accounted for over half of the studies, 89% of patients and 60% of ADRs.[31] Five prospective cohort studies included less than 10% of patients (n=305) but reported one-third of the ADRs.[31] Nine case reports and 2 case series were also included.[31] Glucocorticoids were used to manage various medical conditions, including asthma, bronchiolitis, croup, acute renal failure, allergic rhinitis, dengue

fever, infantile spasms, nephrotic syndrome, acute leukemia, acute idiopathic thrombocytopenic purpura and systemic lupus erythematosus.[31] Prednisolone and dexamethasone were the most commonly used glucocorticoids.[31]

The most serious adverse effect associated glucocorticoids was infection.[31] Five RCTs reported an incidence of infection of 0.9%.[31] Three cases were reported of children infected with varicella zoster, one of whom died and the other 2 were admitted to the intensive care unit with severe complications.[31] In 4 studies, 43 children showed a statistically significant biochemical suppression of the HPA axis.[31] One case series also showed a significant occurrence of transient HPA axis suppression in 3 of 11 children with a 5-day course of prednisolone (2 mg/kg/day).[31] All the children returned to a normal level of endogenous cortisol secretion within 10–12 days after discontinuation of the glucocorticoids.[31]

The 3 most common adverse effects were vomiting, changes in behavior and disturbed sleep.[31] Vomiting was the most common adverse effect with an incidence of 5.4% and was the most frequent reason for early discontinuation of glucocorticoids.[31] Prednisolone sodium phosphate solution was less likely to cause vomiting compared to other formulations (prednisolone base solution and dexamethasone solution).[31] Mood swings and behavioral disturbance were the second most frequently observed adverse events with an incidence of 4.7%. Mood swings (anxiety, hyperactivity and aggressive behavior) were significantly more frequent with higher doses (2 mg/kg/day or 60 mg/m²/day) of prednisolone than with lower doses (1 mg/kg/day).[31] Sleep disturbance was the third most frequent observed adverse event caused by glucocorticoids, with an incidence of 4.3%.[31] Two studies (one RCT and one cohort study) reported 101 children had sleep disturbances.[31] Three studies (one RCT, one cohort study and one case series) evaluated weight changes in patients.[31] Thirty of the 84 patients measured showed weight gain.[31]

After review, 6 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[42-47]

GUIDELINES:
High Quality Guidelines

Asthma

The GINA guidelines were updated in 2020.[32] The recommendations suggest if the initial asthma presentation is severely uncontrolled or an acute exacerbation, start regular controller treatment with medium dose inhaled glucocorticoid combined with a long-acting beta-agonist with as-needed short-acting beta-agonist.[32] Add-on low dose oral glucocorticoids (≤7.5 mg/day prednisone equivalent) may be effective for some adults with severe asthma (Evidence Level D: panel consensus judgement), but are often associated with substantial side effects (Evidence level A: based on rich body of data including RCTs and systematic reviews).[32] Oral glucocorticoids should only be considered for adults with poor symptom control or frequent exacerbations despite good inhaler technique and adherence with guideline-recommended treatment, and after exclusion of other contributory factors and other add-on treatments including biologics.[32] Patients should be counseled about potential side-effects.[32] They should be assessed and monitored for risk of glucocorticoid-induced osteoporosis, and those expected to be treated for 3 months or more should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[32]

Congenital Adrenal Hyperplasia

In November 2018, the Endocrine Society published updated clinical practice guidelines for management of CAH due to steroid 21-hydroxylase deficiency.[33] Congenital adrenal hyperplasia is a group of autosomal recessive disorders characterized by impaired cortisol synthesis.[33] Based on neonatal screening and

national case registries, the worldwide incidence in most studies ranges from ~1:14,000 to 1:18,000 births, but the condition is more prevalent in small, genetically isolated groups with a smaller gene pool, particularly in remote geographic regions (e.g., Alaskan Yupiks).[33] Proper treatment with glucocorticoids prevents adrenal crisis and virilization, allowing nearly normal growth and development during childhood.[33] Management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism.[33]

During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse side effects typical of longer-acting, more potent glucocorticoids, especially growth suppression.[33] Although free-alcohol hydrocortisone suspensions achieve cortisol levels comparable to those achieved by hydrocortisone tablets, hydrocortisone cypionate oral suspensions were inadequate to control CAH in children due to uneven distribution in liquid form.[33] Good control can be achieved by orally administering crushed, weighed hydrocortisone tablets mixed with a small volume of liquid, if needed, immediately before administration.[33] Compounding pharmacies should be chosen for reliability in preparing very small doses or special drug formulations, as there have been reports of variable dose accuracy in compounded preparations.[33]

Patients with severe forms of CAH are unable to produce sufficient cortisol in response to stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma, and therefore, require increased doses of glucocorticoids during such episodes.[33] In contrast to maintenance treatment given 3 times daily, it is recommended that stress dosing be given every 6 hours.[33] Specific recommendations by the Endocrine Society regarding glucocorticoid utilization in the management of CAH include:

- In growing individuals with classic congenital adrenal hyperplasia, use hydrocortisone as maintenance therapy. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In growing individuals with congenital adrenal hyperplasia, avoid the use of oral hydrocortisone suspension and avoid chronic use of long-acting potent glucocorticoids. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In adults with classic congenital adrenal hyperplasia, daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids are recommended, as clinically indicated. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In all individuals with classic congenital adrenal hyperplasia, monitor for signs of glucocorticoid excess, as well as for signs of inadequate androgen normalization, to optimize the adrenal steroid treatment profile. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In pediatric patients with congenital adrenal hyperplasia, conduct regular assessments of growth velocity, weight, blood pressure, physical examinations, and biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid replacement. (Strong Recommendation, Low-Quality Evidence)[33]
- In pediatric patients with congenital adrenal hyperplasia over the age of 2 years, advise annual bone age assessment until near-adult height is attained. (Ungraded Good Practice Statement)[33]
- In adults with congenital adrenal hyperplasia, conduct annual physical examinations, which include assessments of blood pressure, body mass index, and Cushingoid features in addition to obtaining biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid replacement. (Strong Recommendation, Low-Quality Evidence)[33]
- Glucocorticoid maintenance therapy recommendations in fully grown patients with CAH are presented in **Table 2.**

Table 2. Glucorticoid Maintenance Therapy in Fully Grown Patients with Congenital Adrenal Hyperplasia[33]

Glucocorticoid	Suggested Dose (mg/day)	Daily Dosing Regimen
Hydrocortisone	15-25	2-3
Prednisone	5-7.5	2

Prednisolone	4-6	2
Methylprednisolone	4-6	2
Dexamethasone	0.25-0.5	1-2
Abbreviation: mg = milligram		

Chronic Obstructive Pulmonary Disease

According to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, oral glucocorticoids have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.[30] Long-term use of oral glucocorticoids has numerous adverse effects (Evidence A; high quality evidence from 2 or more RCTs) with no evidence of benefits (Evidence C; observational studies).[30] Long-term therapy with oral corticosteroids is not recommended (Evidence A). In an acute COPD exacerbation, systemic corticosteroids improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration.[30] Duration of therapy should not be more than 5-7 days (Evidence A).[30]

Corticosteroids In Pregnancy And Breastfeeding

In 2017 the BSR and BHPR collaborated to update guidance for prescribing glucocorticoids in pregnancy and breastfeeding.[34] These recommendations were part of a series focused on drug safety of immunosuppressive drugs in pregnancy and breast feeding. Recommendations for men trying to conceive with their partner while taking glucocorticoids was also given where sufficient evidence was available.

Four cohort studies and 2 case series reported on outcomes from pregnancies (n=2,127) after paternal exposure to prednisolone and a case-control study and a case series reported on outcomes from pregnancies (n=4) after paternal exposure to methylprednisolone.[7] Overall, the quality of these studies was low, but, they did not identify an increased risk of adverse fetal outcomes.[34] Evidence for safe use of glucocorticoids in pregnancy was obtained from 47 studies on prednisolone (n=1503 pregnancies); 31 studies on dexamethasone (n=11,214 pregnancies); 27 studies on betamethasone (n=27,746 pregnancies); and 10 on general corticosteroids (n=785 pregnancies).[34] Types of studies included RCTs, systematic reviews, cohort studies, case-control studies, and case reports. The studies were confounded by multiple concomitant medications which are used to prevent or treat preterm labor and complications such as fetal lung immaturity.[34] Prednisolone, prednisone and methylprednisolone are metabolized in the placenta, so 10% or less of the active drug reaches the fetus, and they are considered to be compatible with pregnancy and breastfeeding.[34] Grading recommendations were based on the Scottish Intercollegiate Guidelines Network (SIGN) as follows:[48]

- Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy (Level of Evidence: 1++, based on high quality meta-analyses, systematic reviews or RCTs with low risk of bias; Grade of Recommendation: A, based on at least 1 meta-analysis, systematic review or high quality RCT directly applicable to target population).[34]
- Prednisolone is compatible with breastfeeding (Level of Evidence: 2-, case control or cohort studies with high risk of confounding; Grade of Recommendation: D, based on extrapolated evidence from case reports or expert opinion).[34]
- Prednisolone is compatible with paternal exposure (Level of Evidence: 2+, based upon well conducted case-control or cohort studies with low risk of confounding; Grade of Recommendation D, based upon extrapolated evidence from case reports or expert opinion).[34]

Hypopituitarism in Adults

In 2016 the Endocrine Society formulated clinical practice guidelines for hormonal replacement in adults with hypopituitarism.[35] The guideline Task Force commissioned two systematic reviews to assist with summarizing the evidence base for this guideline.[35] Hypopituitarism results from complete or partial

deficiency in pituitary hormones and includes adrenal insufficiency, hypothyroidism, hypogonadism, growth hormone deficiency, and (more rarely) diabetes insipidus.[35] Hypopituitarism is the consequence of diseases that either reduce or destroy secretory function or interfere with the hypothalamic secretion of pituitary-releasing hormones.[35] Central adrenal insufficiency represents inadequate cortisol secretion due to ACTH deficiency. It can be secondary, when pituitary disease impairs the release of ACTH, or tertiary from inadequate hypothalamic corticotropin-releasing hormone.[35] Glucocorticoid replacement is just one aspect of the multi-pronged approach to managing this condition. Specific recommendations include:

- Hydrocortisone is recommended, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regimen) or the second and third at lunch and late afternoon, respectively (three-dose regimen). (Strong Recommendation, Moderate-Quality Evidence).[35]
- It is suggested to use longer-acting glucocorticoids in selected cases (e.g., nonavailability, poor compliance, convenience). (Weak Recommendation; Low-Quality Evidence).[35]
- Clinicians should teach all patients with adrenal insufficiency regarding stress-dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit containing injectable high-dose glucocorticoid (Strong Recommendation; Moderate-Quality Evidence).[35]
- It is suggested to test HPA axis functionality before and after starting GH replacement in patients who are not receiving glucocorticoid replacement and who have demonstrated apparently normal pituitary-adrenal function (Weak Recommendation; Low-Quality Evidence).[35]
- Clinicians should assess adrenal reserve or the adequacy of HC replacement, and take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on glucocorticoid-binding globulin (CBG). (Weak Recommendation; High-Quality Evidence).[35]
- Clinicians should individually assess glucocorticoid replacement and avoid over-replacement to reduce the risk of osteoporosis. Low-dose hydrocortisone replacement is recommended because this approach might be associated with increased bone formation and a positive bone-remodeling balance (Weak Recommendation; Low-Quality Evidence).[35]

<u>Primary Adrenal Insufficiency (Addison' Disease)</u>

The Endocrine Society published clinical guidelines that address the diagnosis and treatment of PAI in 2016.[36] Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids.[36] Primary adrenal insufficiency is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt, and fluid homeostasis.[36] Except for salt craving, the symptoms of PAI are rather nonspecific and include weakness, fatigue, musculoskeletal pain, weight loss, abdominal pain, depression, and anxiety.[36] As a result, the diagnosis is frequently delayed, resulting in a clinical presentation with an acute life-threatening adrenal crisis.[36] Primary adrenal insufficiency is a rare disease with a reported prevalence of about 100 to 140 cases per million and an incidence of 4:1,000,000 per year in Western societies.[36] The most common cause of PAI is autoimmunity (up to 90% in Western countries), followed by infectious diseases such as tuberculosis, adrenalectomy, neoplasia, and various genetic causes. Genetic causes are more likely to be present and diagnosed in children.[36] Glucocorticoid replacement regimen recommendations include:

- Start glucocorticoid therapy in all patients with confirmed PAI. (Moderate Recommendation; High-Quality Evidence)[36]
- Use hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day; the highest dose should be given in the morning at awakening, the next either in the early afternoon (2 h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be beneficial in individual cases. (Weak Recommendation; Low-Quality Evidence)[36]
- As an alternative to hydrocortisone, prednisolone (3–5 mg/day), administered orally once or twice daily, especially in patients with reduced compliance. (Weak Recommendation; Very Low-Quality Evidence)[36]

- Dexamethasone is not suggested for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration. (Weak Recommendation; Low-Quality Evidence)[36]
- It is advised to monitor glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess. (Weak Recommendation; Moderate-Quality Evidence)[36]
- In children with PAI, treatment with hydrocortisone is suggested in 3 or 4 divided doses (total starting daily dose of 8 mg/m^2 body surface area) over other types of glucocorticoid replacement therapies, with doses adjusted according to individual need. (Weak Recommendation; Low-Quality Evidence)[36]
- In children with PAI, avoid synthetic, long-acting glucocorticoids (e.g., prednisolone, dexamethasone). (Weak Recommendation; Low-Quality Evidence)[36]
- Monitor glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure, and energy levels. (Ungraded Best Practice Statement)[36]
- Pregnant patients with PAI should be monitored for clinical symptoms and signs of glucocorticoid over- and under-replacement (e.g., normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia), with at least one review per trimester. (Ungraded Best Practice Statement)[36]
- Based on the individual clinical course, an increase in hydrocortisone dose should be implemented, in particular during the third trimester. (Ungraded Best Practice Statement)[36]
- In pregnant women with PAI, use hydrocortisone over cortisone acetate, prednisolone, or prednisone (Weak Recommendation; Low-Quality Evidence) and recommend against using dexamethasone because it is not inactivated in the placenta. (Strong Recommendation; Low-Quality Evidence)[36]
- Hydrocortisone stress dosing is recommended during the active phase of labor, similar to that used in major surgical stress. (Strong Recommendation; Low-Quality Evidence)[36]

After review, 1 guideline was excluded due to poor quality.[49]

Randomized Controlled Trials:

A total of 207 citations were manually reviewed from the initial literature search. After further review, 205 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Paniagua et al.[50] OL,NI,RCT	1. Dexamethasone 0.6 mg/kg x 2 doses x 1 day 2. Prednisone 1.5 mg/kg/day x 1 day followed by 1 mg/kg/day x 4 days	Children aged 1-14 years old with Acute Asthma Exacerbation n=557	Percentage of patients with asthma symptoms and quality of life at day 7 assessed via telephonic consultation using PACT and ARQoL scales	Persistence of Symptoms (PACT) 1. 56.6% 2. 58.3% P=NS Mean Quality of Life score (ARQoL) 1. 80.0 2. 77.7 P=NS	• OL, NI design of study can lead to bias • Primary outcomes were based on subjective assessments reported by parents of the enrolled children • 43% of children were under 5 years of age, which may have made it difficult to

					assess self-reporting of symptoms • Adherence rates not assessed
Burmester G, et al.[51] DB, MC, RCT	1.Prednisone 5 mg/day x 24 weeks 2.Taper prednisone to 0 mg/day over 16 weeks	Adults with RA receiving tocilizumab and glucocorticoids 5-15 mg/day x 24 weeks or more with low disease activity (DAS28-ESR score $\leq$ 3.2) N=259	Difference in mean DAS28-ESR change from baseline to week 24	Mean change in DAS28-ESR from baseline to week 24: 1. -0.08 2. 0.54 Difference: 0.61; 95% CI: 0.35 to 0.88; p<0.0001 *Change in DAS28-ESR of 0.6 units considered clinically relevant	• Relatively short-term trial (6 months) • Cannot extrapolate results to patients taking different glucocorticoid doses or other RA treatments • Bone mineral density not assessed
Mathian A, et al.[52] OL, RCT	1.Prednisone 5 mg/day x 52 weeks 2. Prednisone withdrawal on Day 0, patients started on hydrocortisone 20 mg/day to prevent adrenal failure	Adult SLE patients who, during the year preceding the inclusion, had a clinically inactive disease and a stable SLE treatment including 5 mg/day prednisone N=124	Proportion of patients experiencing a flare defined with the SELENA-SLEDAI flare index at 52 weeks.	Proportion of patients experiencing a flare at 52 weeks: 1. 4/61 (7%) 2. 17/63 (27%) RR 0.2; 95% CI 0.1 to 0.7; P=0.003	• OL trial without a placebo group • Withdrawal of 5 mg of prednisone was relatively abrupt, cannot exclude possibility that slow prednisone tapering would have resulted in less flares. • Inclusion bias may have confounded results: the SLE patients were kept on low dose of steroids by their treating physician despite clinical remission. It is possible that these patients had a special lupus history with severe flares, major organ involvements and relapses that prompted the physician to maintain this long-term treatment.

Abbreviations: ARQoL=Asthma-Related Quality of Life tool; CI=confidence interval; DAS28-ESR=28 joint Disease Activity Score-Erythrocyte Sedimentation Rate; DB=double-blind; kg=kilogram; MC=multi-center; mg=milligram; NI=Non-inferiority; OL=open label; PACT= Pediatric Asthma Control Tool; RA=rheumatoid arthritis; RCT=randomized clinical trial; RR=RR; SLE=systemic lupus erythematosus					

Recent FDA-approved Indications and Formulations

- A new oral formulation of dexamethasone (HEMADY) received FDA approval October 2019.[53] This product is available as a 20 mg tablet and is indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma.[53] The recommended dose is 20 or 40 mg once daily, on specific days depending on the protocol regimen.[53]
- A new formulation of hydrocortisone (ALKINDI SPRINKLE) received FDA approval September 2020. This product is indicated as replacement therapy in pediatric patients with adrenocortical insufficiency.[54] The recommended starting replacement dosage is 8 to 10 mg/m^2 daily.[54] Higher doses may be needed based on patient's age and symptoms of the disease.[54] Use of lower starting doses may be sufficient in patients with residual but decreased endogenous cortisol production.[54] Use of hydrocortisone sprinkles in pediatric patients is supported by use of another hydrocortisone product in pediatric patients with adrenocortical insufficiency and supportive pharmacokinetic and safety data in 24 pediatric patients with adrenocortical insufficiency.[54]

References:

1. Buchbinder R, Green S, Youd JM, Johnston RV. Oral steroids for adhesive capsulitis. *Cochrane Database Syst Rev.* 2006(4).
2. Kornelsen E, Mahant S, Parkin P, et al. Corticosteroids for periorbital and orbital cellulitis. *Cochrane Database Syst Rev.* 2021(4).
3. Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev.* 2019(2).
4. Janssens HJ, Lucassen P, Van de Laar FA, Janssen M, Van de Lisdonk EH. Systemic corticosteroids for acute gout. *Cochrane Database Syst Rev.* 2008(2).
5. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. *Cochrane Database Syst Rev.* 2017(3).
6. Ranakusuma RW, Pitoyo Y, Safitri ED, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database Syst Rev.* 2018;3(3):Cd012289.
7. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev.* 2005(2).
8. Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. *Cochrane Database Syst Rev.* 2015(8):CD001430.
9. Hughes RAC, Mehndiratta MM, Rajabally YA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev.* 2017(11).
10. Head K, Chong LY, Hopkins C, Philpott C, Burton MJ, Schilder AG. Short-course oral steroids alone for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016;4:CD011991.
11. Head K, Chong LY, Hopkins C, Philpott C, Schilder AG, Burton MJ. Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016;4:CD011992.
12. Paramothayan NS, Lasserson TJ, Jones P. Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev.* 2005(2).
13. Prince M, Christensen E, Gluud C. Glucocorticosteroids for primary biliary cirrhosis. *Cochrane Database Syst Rev.* 2005(2).
14. Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. *Cochrane Database Syst Rev.* 2020(3).
15. Zhang F, Kramer CV. Corticosteroids for dengue infection. *Cochrane Database Syst Rev.* 2014(7).
16. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev.* 2015(4).
17. Haywood A, Duc J, Good P, et al. Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults. 2019;1:Cd012704.
18. Chen HS, Wang W, Wu S, Liu JP. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev.* 2013(10).
19. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev.* 2013(3).
20. de Cassan S, Thompson MJ, Perera R, et al. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database Syst Rev.* 2020;5(5):Cd008268.
21. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *Journal of Asthma.* 2019;56(12):1334-1346.
22. Venekamp RP, Thompson MJ, Hayward G, et al. Systemic corticosteroids for acute sinusitis. [Review]. 2014;1(3):Cd008115.
23. Gates A, Gates M, Vandermeer B, et al. Glucocorticoids for croup in children. *Cochrane Database Syst Rev.* 2018(8).
24. Madhok VB, Gagyor I, Daly F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev.* 2016(7).

25. Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. *Cochrane Database Syst Rev.* 2015(12):CD000407.
26. Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane Database Syst Rev.* 2012(12).
27. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2007(3).
28. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis care & research.* 2017;69(8):1095-1110.
29. Chang YP, Lai CH, Lin CY, et al. Mortality and vertebral fracture risk associated with long-term oral steroid use in patients with chronic obstructive pulmonary disease: A systemic review and meta-analysis. *Chron Respir Dis.* 2019;16:1479973119838280.
30. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *American journal of respiratory and critical care medicine.* 2017;195(5):557-582.
31. Aljebab F, Choonara I, Conroy S. *Archives of Disease in Childhood.* 2016;101(4):365-370.
32. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginasthma.org. Accessed November 8, 2021.
33. Speiser PW, Arlt W, Auchus RJ, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2018;103(11):4043-4088.
34. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology.* 2016;55(9):1693-1697.
35. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2016;101(11):3888-3921.
36. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism.* 2016;101(2):364-389.
37. Dineen R, Stewart PM, Sherlock M. Factors impacting on the action of glucocorticoids in patients receiving glucocorticoid therapy. *Clin Endocrinol (Oxf).* 2019;90(1):3-14.
38. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol.* 2013;9(1):30.
39. Overman RA, Yeh J-Y, Deal CL. Prevalence of oral glucocorticoid usage in the United States: A general population perspective. *Arthritis care & research.* 2013;65(2):294-298.
40. Williams DM. Clinical Pharmacology of Corticosteroids. *Respir Care.* 2018;63(6):655-670.
41. Hughes RAC, Brassington R, Gunn AA, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. *Cochrane Database Syst Rev.* 2016(10).
42. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *American journal of respiratory and critical care medicine.* 2020;201(3):276-293.
43. Deng J, Silver Z, Huang E, et al. Pharmacological prevention of fractures in patients undergoing glucocorticoid therapies: a systematic review and network meta-analysis. *Rheumatology (Oxford, England).* 2021;60(2):649-657.
44. Bonovas S, Nikolopoulos GK, Lytras T, Fiorino G, Peyrin-Biroulet L, Danese S. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis. *Br J Clin Pharmacol.* 2018;84(2):239-251.

45. Castro-Rodriguez JA, Beckhaus AA, Forno E. Efficacy of oral corticosteroids in the treatment of acute wheezing episodes in asthmatic preschoolers: Systematic review with meta-analysis. *Pediatric pulmonology.* 2016;51(8):868-876.
46. Gøtzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev.* 2005(1).
47. Fernandes RM, Wingert A, Vandermeer B, et al. Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis. *BMJ Open.* 2019;9(8):e028511.
48. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ (Clinical research ed).* 2001;323(7308):334-336.
49. Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *Bmj.* 2017;358:j4090.
50. Paniagua N, Lopez R, Muñoz N, et al. Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations. *The Journal of pediatrics.* 2017;191:190-196.e191.
51. Burmester GR, Buttgereit F, Bernasconi C, et al. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet (London, England).* 2020;396(10246):267-276.
52. Mathian A, Pha M, Haroche J, et al. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. *Ann Rheum Dis.* 2020;79(3):339-346.
53. HEMADY (dexamethasone) oral tablets. Prescribing Information. Acrotech Biopharma; East Windsor, NJ. June 2021.
54. ALKINDI SPRINKLE (hydrocortisone) oral granules. Prescribing Information. Eton Pharmaceuticals, Deer Park, IL. September 2020.
55. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed November 1, 2021.
56. Lexicomp Online. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed November 1, 2021.

Appendix 1. Oral Glucocorticoid Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics[55,56]

Drug Name	Mechanism of Action	Absorption	Metabolism	Excretion	• **Half Life** • **Volume of Distribution**
Short-acting					
Hydrocortisone	Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability	Bioavailability: 96% Protein Binding: 92%	Hepatic	Renal	• 1.5-2 hours • 0.5 L/kg
Cortisone		Bioavailability: 44% Protein Binding: 90%	Hepatic: to active metabolite hydrocortisone	Renal	• 0.5 hours • NR
Intermediate-acting					
Prednisone	Suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses	Bioavailability: 50-90% Protein Binding: 50%	Hepatic: to active metabolite prednisolone	Renal	• 2-3 hours • 0.4 -1 L/kg
Prednisolone		Bioavailability: 84-96% Protein Binding: 70-90%	Hepatic	Renal	• 2-4 hours • 0.22-0.7 L/kg
Methylprednisolone		Bioavailability: 88% Protein Binding: NR	Hepatic	Renal	• 2-3 hours • 1.5 L/kg
Long-acting					
Dexamethasone	Decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response	Bioavailability: 61-86% Protein Binding: 77%	Hepatic	Renal	• 4 hours • NR
Abbreviations: kg =kilogram; L=Liter; NR=not reported					

Drug Safety

Use in Specific Populations:

- Elderly: Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. Steroid psychosis is more common in elderly patients, especially in those who are terminally ill.[56]

- Pediatric: May affect growth velocity; growth should be routinely monitored in pediatric patients.[56]
- Pregnancy: Some studies have shown an association between first trimester systemic glucocorticoid use and oral clefts. Systemic glucocorticoids may also influence fetal growth (decreased birth weight); however, information is conflicting. When systemic glucocorticoids are needed in pregnancy, it is generally recommended to use the lowest effective dose for the shortest duration of time, avoiding high doses during the first trimester.[56]
- Breast feeding: Glucocorticoids are excreted in breast milk. The manufacturer notes that when used systemically, maternal use of glucocorticoids have the potential to cause adverse events in a breastfeeding infant (e.g., growth suppression, interference with endogenous glucocorticoid production). Prednisone is one of the oral glucocorticoids preferred for use in breastfeeding women. Breastfeeding is acceptable for patients with rheumatic and musculoskeletal diseases taking prednisone <20 mg/day.[56]

Boxed Warnings and Risk Evaluation Mitigation Strategy (REMS) Programs: None of the glucocorticoid formulations have FDA boxed warnings or REMS programs.

Contraindications:

- Immunizations: Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of glucocorticoids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted.[56]
- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.[56]
- May cause osteoporosis (at any age) or inhibition of bone growth in pediatric patients. Use with caution in patients with osteoporosis; high doses and/or long-term use of glucocorticoids have been associated with increased bone loss and osteoporotic fractures.[56]
- Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose glucocorticoids should not be used for the management of head injury.[56]

Table 2. Summary of Warnings and Precautions[56]

Warning/Precaution	Hydrocortisone	Cortisone	Prednisone	Prednisolone	Methylprednisolone	Dexamethasone
Adrenal Suppression	x	x	x	x	x	x
Psychiatric Effects	x	x	x	x	x	x
Cushingoid Features	x	x	x	x	x	x
Gastrointestinal Effects	x	x	x	x	x	x
Hyperglycemia	x	x	x	x	x	x
Infection	x	x	x	x	x	x
Neuromuscular and Skeletal Effects	x	x	x	x	x	x
Ocular Effects	x	x	x	x	x	x

Appendix 2: Current Preferred Drug List and Specific Drug Information

Generic	Brand	Route	Form
cortisone acetate	CORTISONE ACETATE	ORAL	TABLET
dexamethasone	DEXAMETHASONE INTENSOL	ORAL	DROPS
dexamethasone	DEXAMETHASONE	ORAL	ELIXIR
dexamethasone	DEXAMETHASONE	ORAL	SOLUTION
dexamethasone	DEXAMETHASONE	ORAL	TAB DS PK
dexamethasone	TAPERDEX	ORAL	TAB DS PK
dexamethasone	DEXAMETHASONE	ORAL	TABLET
dexamethasone	HEMADY	ORAL	TABLET
hydrocortisone	ALKINDI SPRINKLE	ORAL	CAP SPRINK
hydrocortisone	CORTEF	ORAL	TABLET
hydrocortisone	HYDROCORTISONE	ORAL	TABLET
methylprednisolone	MEDROL	ORAL	TAB DS PK
methylprednisolone	METHYLPREDNISOLONE	ORAL	TAB DS PK
methylprednisolone	MEDROL	ORAL	TABLET
methylprednisolone	METHYLPREDNISOLONE	ORAL	TABLET
prednisolone	PREDNISOLONE	ORAL	SOLUTION
prednisolone	MILLIPRED	ORAL	TABLET
prednisolone sodium phosphate	PEDIAPRED	ORAL	SOLUTION
prednisolone sodium phosphate	PREDNISOLONE SODIUM PHOSPHATE	ORAL	SOLUTION
prednisolone sodium phosphate	PREDNISOLONE SODIUM PHOS ODT	ORAL	TAB RAPDIS
prednisone	PREDNISONE INTENSOL	ORAL	ORAL CONC
prednisone	PREDNISONE	ORAL	SOLUTION
prednisone	PREDNISONE	ORAL	TAB DS PK
prednisone	PREDNISONE	ORAL	TABLET
prednisone	RAYOS	ORAL	TABLET DR

Appendix 3: Abstracts

Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations[50]

Objective: To determine whether 2 doses of dexamethasone is as effective as 5 days of prednisolone/prednisone therapy in improving symptoms and quality of life of children with asthma exacerbations admitted to the emergency department (ED).

Study design: We conducted a randomized, noninferiority trial including patients aged 1-14 years who presented to the ED with acute asthma to compare the efficacy of 2 doses of dexamethasone (0.6 mg/kg/dose, experimental treatment) vs a 5-day course of prednisolone/prednisone (1.5 mg/kg/d, followed by 1 mg/kg/d on days 2-5, conventional treatment). Two follow-up telephone interviews were completed at 7 and 15 days. The primary outcome measures were the percentage of patients with asthma symptoms and quality of life at day 7. Secondary outcomes were unscheduled returns, admissions, adherence, and vomiting.

Results: During the study period, 710 children who met the inclusion criteria were invited to participate and 590 agreed. Primary outcome data were available in 557 patients. At day 7, experimental and conventional groups did not show differences related to persistence of symptoms (56.6%, 95% CI 50.6-62.6 vs 58.3%, 95% CI 52.3-64.2, respectively), quality of life score (80.0 vs 77.7, not significant [ns]), admission rate (23.9% vs 21.7%, ns), unscheduled ED return visits (4.6% vs 3.3%, ns), and vomiting (2.1% vs 4.4%, ns). Adherence was greater in the dexamethasone group (99.3% vs 96.0%, P < .05).

Conclusion: Two doses of dexamethasone may be an effective alternative to a 5-day course of prednisone/prednisolone for asthma exacerbations, as measured by persistence of symptoms and quality of life at day 7.

Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial[51]

Background: Patients with inflammatory diseases, such as rheumatoid arthritis, often receive glucocorticoids, but long-term use can produce adverse effects. Evidence from randomised controlled trials to guide tapering of oral glucocorticoids is scarce. We investigated a scheme for tapering oral glucocorticoids compared with continuing low-dose oral glucocorticoids in patients with rheumatoid arthritis.

Methods: The Steroid EliMination In Rheumatoid Arthritis (SEMIRA) trial was a double-blind, multicentre, two parallel-arm, randomised controlled trial done at 39 centres from six countries (France, Germany, Italy, Russia, Serbia, and Tunisia). Adult patients with rheumatoid arthritis receiving tocilizumab and glucocorticoids 5-15 mg per day for 24 weeks or more were eligible for inclusion if they had received prednisone 5 mg per day for 4 weeks or more and had stable low disease activity, confirmed by a Disease Activity Score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR) of 3·2 or less 4-6 weeks before and on the day of randomization. Patients were randomly assigned 1:1 to either continue masked prednisone 5 mg per day for 24 weeks or to taper masked prednisone reaching 0 mg per day at week 16. All patients received tocilizumab (162 mg subcutaneously every week or 8 mg/kg intravenously every 4 weeks) with or without csDMARDs maintained at stable doses during the entire 24-week study. The primary outcome was the difference in mean DAS28-ESR change from baseline to week 24, with a difference of more than 0·6 defined as clinically relevant between the continued-prednisone group and the tapered-prednisone group. The trial is registered with ClinicalTrials.gov, NCT02573012.

Findings: Between Oct 21, 2015, and June 9, 2017, 421 patients were screened and 259 (200 [77%] women and 59 [23%] men) were recruited onto the trial. In all 128 patients assigned to the continued-prednisone regimen, disease activity control was superior to that in all 131 patients assigned to the tapered-prednisone regimen; the estimated mean change in DAS28-ESR from baseline to week 24 was 0·54 (95% CI 0·35-0·73) with tapered prednisone and -0·08 (-0·27 to 0·12) with continued prednisone (difference 0·61 [0·35-0·88]; p<0·0001), favoring continuing prednisone 5 mg per day for 24 weeks. Treatment was regarded as successful (defined as low disease activity at week 24, plus absence of rheumatoid arthritis flare for 24 weeks and no confirmed adrenal insufficiency) in 99 (77%) patients in the continued-prednisone group versus 85 (65%) patients in the tapered-prednisone group (relative risk 0·83; 95% CI 0·71-0·97). Serious adverse events occurred in seven (5%) patients in the tapered-prednisone group and four (3%) patients in the continued-prednisone group; no patients had symptomatic adrenal insufficiency.

Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial[52]

Objectives: To compare the efficacy to prevent flares of maintenance versus withdrawal of 5 mg/day prednisone in systemic lupus erythematosus (SLE) patients with clinically quiescent disease.

Methods: A monocentric, 12-month, superiority, open-label, randomised (1:1) controlled trial was conducted with 61 patients continuing 5 mg/day prednisone and 63 stopping it. Eligibility criteria were SLE patients who, during the year preceding the inclusion, had a clinically inactive disease and a stable SLE treatment including 5 mg/day prednisone. The primary endpoint was the proportion of patient experiencing a flare defined with the SELENA-SLEDAI flare index (SFI) at 52 weeks. Secondary endpoints included time to flare, flare severity according to SFI and British Isles Lupus Assessment Group (BILAG) index and increase in the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI).

Results: Proportion of patients experiencing a flare was significantly lower in the maintenance group as compared with the withdrawal group (4 patients vs 17; RR 0.2 (95% CI 0.1 to 0.7), p=0.003). Maintenance of 5 mg prednisone was superior with respect to time to first flare (HR 0.2; 95% CI 0.1 to 0.6, p=0.002), occurrence of mild/moderate flares using the SFI (3 patients vs 12; RR 0.2 (95% CI 0.1 to 0.8), p=0.012) and occurrence of moderate/severe flares using the BILAG index (1 patient vs 8; RR 0.1 (95% CI 0.1 to 0.9), p=0.013). SDI increase and adverse events were similar in the two treatment groups. Subgroup analyses of the primary endpoint by predefined baseline characteristics did not show evidence of a different clinical response.

Conclusion: Maintenance of long term 5 mg prednisone in SLE patients with inactive disease prevents relapse.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 5 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 12, 2021

1.	exp Cortisone/tu [Therapeutic Use]	280
2.	exp Dexamethasone/tu [Therapeutic Use]	7229
3.	exp Hydrocortisone/tu [Therapeutic Use]	2364
4.	exp Methylprednisolone/tu [Therapeutic Use]	7136
5.	exp Prednisolone/tu [Therapeutic Use]	16744
6.	exp Prednisone/tu [Therapeutic Use]	11048
7.	1 or 2 or 3 or 4 or 5 or 6	36040
8.	limit 7 to (english language and humans)	29959
9.	limit 8 to (yr="2000 -Current" and (clinical trial, phase iii or guideline or meta-analysis or randomized controlled trial or "systematic review"))	2918
10.	Administration, Oral/	99903
11.	9 and 10	207