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 4th, 2021 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Election of Chair/Vice Chair	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Agenda and Minutes	R. Citron (OSU)
	E. Department Update	D. Weston (OHA)
	F. Legislative Update	T. Douglass (OHA)
1:25 PM	II. CONSENT AGENDA TOPICS	Chair
	A. P&T Methods	
	B. Orphan Drug PA Update	
	C. Oncology PA Update	
	D. Anticoagulant Literature Scan	
	1. Public Comment	
	III. DUR ACTIVITIES	
1:30 PM	A. Quarterly Utilization Report	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (GT)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. New Disease-Modifying Anti-Rheumatic Drugs for Management of Rheumatoid Arthritis	
	2. Cardiovascular Outcomes Associated with Newer Therapy Classes for Type 2 Diabetes Mellitus	
	IV. PREFERRED DRUG LIST NEW BUSINESS	
1:50 PM	A. Duchenne Muscular Dystrophy Class Update and DERP Report with New Drug Evaluation	S. Servid (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Viltolarsen (Viltepso®) New Drug Evaluation	

	3. Public Comment 4. Discussion of Clinical Recommendations to OHA	
2:10 PM	B. Acne Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Clascoterone (Winlevi®) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Fletcher (OSU)
2:25 PM	C. Treatments for Peanut Allergy 1. DERP Report/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Fletcher (OSU)
2:40 PM	D. Tobacco Smoking Cessation Literature Scan 1. Literature Scan/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
2:55 PM	BREAK	
3:10 PM	E. Antidepressants Class Update 1. Class Update/Safety Edit 2. MHCAG Meeting Minutes 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:30 PM	F. NSAID Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:50 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
Tim Langford, PharmD, BCPS, CDE, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Oregon Health Forum	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, December 03, 2020 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: Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; William Origer, MD; Mark Helm, MD, MBA, FAAP; James Slater, PharmD; Russell Huffman, DNP, PMHNP; Jim Rickards, MD, MBA; Cathy Zehrung RPh; Patrick DeMartino, MD; Stacy Ramirez, PharmD

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

Audience: Shirley Quach*, Novartis Pharma; Amy Burns, Allcare; Andrea Willcuts, Takeda; Bill McDougal, Biogen; Bruce Wallace, Azurity; Camille Kerr, Regeneron; Chi Kohlhoff, Viela Bio; Deron Grothe, Teva Pharmaceuticals; George Kitchens, Artia Solutions; Jeff Mussack, Braeburn; Jennifer Shear, Teva Pharmaceuticals; Jenny Tofenhagen, Genentech; Katie Scheelar, Moda; **Steve Hall*, Genentech;** Kelly Wright; Lori McDermott, Supernus; Maggi Olmon, Abbvie; Mark Kantor, AllCare Health; Matt Bradley, Novartis; Matt Worthy, OHSU; Timothy McFerron, Alkermes; Micheal Foster, BMS; Mike Findlien, Otsuka Pharma; Paul Thompson, Alkermes; Rachel Hartman, IHN; Rick Frees, Vertex; Rosalynde Finch, Biogen; Roy Linfield, Sunovion; Suzanne Gauen, Providence; Tina Hartmann, Jazz Pharma; **Rebecca Persinger*, Horizon Therapeutics**; Patrick Moby; **Judy Bachman*; Paul Bachman***

(*) Provided verbal testimony

Written testimony: Posted to OSU Website

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I. CALL TO ORDER

A. The meeting was called to order at approximately 1:06 pm. Introductions were made by Committee members and staff
B. Conflict of Interest Declaration - No new conflicts of interest were declared
C. Approval of October 2020 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor
D. Department Update provided by Trevor Douglass

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
B. CMS Annual Report
C. P&T Annual Report
D. Oncology Policy Update
E. Drug Class Literature Scans
   a. Substance Use Disorder, Opioid and Alcohol
   b. Newer Antiemetics

Recommendations:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

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

III. DUR ACTIVITIES

A. ProDUR Report: Rich Holsapple, RPh
B. RetroDUR Report: Dave Engen, PharmD
C. Oregon State Drug Review: Kathy Sentena, PharmD
   - Optimizing use of NPH Insulin in Patient with Type 2 Diabetes Mellitus
   - Shifts in the Treatment of Community Acquired Pneumonia

IV. DUR OLD BUSINESS

A. **Asthma/COPD Drug Class Prior Authorization Update**: Kathy Sentena, PharmD
Recommendation:
   - Modify ICS/LABA/LAMA PA criteria with updated indication for Trelegy Ellipta

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

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B. **Inflammatory Skin Conditions Update**: Deanna Moretz PharmD
Recommendation:
- Revise criteria for biologic therapies, dupilumab, atopic dermatitis and topical antipsoriatics to include the assessment of severe disease using validation scoring tool (i.e. DLQI, CDLQI) per HERC guidance

Public Comments: Shirley Quach, Novartis
ACTION: Motion to approve, 2nd, all in favor

V. PREFERRED DRUG LIST NEW BUSINESS

A. **Sedative Class Update:** Andrew Gibler, PharmD
Recommendations:

- Recommend OHA cover melatonin and make preferred on the PDL
- Update clinical prior authorization criteria
- Evaluate costs in executive session

ACTION: The Committee recommended to not require prior authorization for 18 years of age and under
Motion to approve, 2nd, all in favor

B. **Teprotumumab New Drug Evaluation**: Sara Fletcher, PharmD
Recommendations:
- Designate teprotumumab as non-preferred on the PDL
- Implement proposed clinical PA

Public Comment: Rebecca Persinger, Horizon Therapeutics; Judy Bachman & Paul Bachman
ACTION: Motion to approve, 2nd, all in favor

C. **Gout Agents Class Update**: Kathy Sentena, PharmD
Recommendation:
- No changes to PDL base on clinical evidence
- Update PA criteria to allow colchicine in patient with pericarditis and Behçet's Syndrome
- Evaluate costs in executive session

ACTION: The Committee recommended allowing a small quantity without PA
Motion to approve, 2nd, all in favor

D. **Risdiplam New Drug Evaluation:** Dave Engen, PharmD
Recommendation:
- Add risdiplam to PDL and designate as non-preferred

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- Implement proposed PA criteria

ACTION: The Committee recommended adding a request for baseline pulmonary function and a follow up question in the renewal criteria
Motion to approve, 2nd, all in favor

E. **Cenegermin New Drug Evaluation:** Megan Herink, PharmD
Recommendation:
- Designate Cenegermin as non-preferred on the PDL
- Implement proposed PA criteria

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

VI. DUR NEW BUSINESS

A. **Drug Discontinuation Safety Net Policy Proposal:** Sarah Servid, PharmD
Recommendation:
- Implement a case management referral program for patients with gaps in care for high risk maintenance medications

ACTON: **Motion to approve, 2nd, all in favor**

B. **Consultation for Antipsychotic in Children Policy Evaluation**: Sarah Servid, PharmD
Recommendation:
- Continue to monitor drug therapy changes after referral and consultation for pediatric patients on long-term antipsychotics

ACTON: **Motion to approve, 2nd, all in favor**

VII. EXECUTIVE SESSION

Members Present: Tracy Klein, PhD, FNP; William Origer, MD; Mark Helm, MD, MBA, FAAP; James Slater, PharmD; Russell Huffman, DNP, PMHNP; Cathy Zehrung RPh; Patrick DeMartino, MD; Stacy Ramirez, PharmD

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

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VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Substance Use Disorder**:
Recommendation: No changes to the PDL are recommended

B. **Newer Antiemetics:**
Recommendation: No changes to the PDL are recommended

C. **Sedatives:**
Recommendation: Make melatonin tablets and similarly priced generic products preferred pending OHA state plan amendment

D. **Gout:**
Recommendation: Make Colcrys preferred on the PDL

E. **CGRP Inhibitors:**
Recommendation: Make Ajovy preferred on PDL

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

IX. ADJOURN

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
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Review Standards and Methods for Quality Assessment of Evidence
Updated: February 2021~~0~~

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 *(If bolded assessments are not met (i.e. the answer is "No") the trial will be excluded from DURM reviews)	
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:

- □ Population
- □ Intervention
- □ Comparator group
- □ Outcome

Optional (recommended)

- □ Timeframe for follow-up

□ Yes
□ No

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:

- □ review question(s)
- □ a search strategy
- □ inclusion/exclusion criteria
- □ a risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:

- □ a meta-analysis/synthesis plan, if appropriate, and
- □ a plan for investigating causes of heterogeneity
- □ justification for any deviations from the protocol

□ Yes
□ Partial Yes
□ No

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:

- □ Explanation for including only RCTs
- □ OR Explanation for including only NRSI
- □ OR Explanation for including both RCTs and NRSI

□ Yes
□ No

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)*

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: February 2021~~0~~

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.

~~5.~~7. Guide and approve meeting agendas.

~~6.~~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

Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
Lonafarnib	ZOKINVY
Lumasiran	OXLUMO

Recommendation:

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

Appendix 1. Proposed Prior Authorization Criteria

Orphan Drugs

Goal(s):
- To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions
- To limit off-label use of orphan drugs

Length of Authorization:
- Up to 6 months

Requires PA:
- See Table 1 (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. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 months TIO ≥ 2 years	Pediatric <18 years: Initial (administered SC every 2 weeks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels

			2 mg/kg or 180mg every 2 weeks)	• Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 years	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 years	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation	≥12 months AND ≥0.39 m^2 body surface area	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)

	○ Homozygous or compound heterozygous ZMPSTE24 mutations			
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels	Adult and pediatric patients	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months **≥ 20 kg** Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hg <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions	≥ 18 years	Initial: 1 mg/kg subcutaneously Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 weeks in patients with myelodysplastic syndromes

	Anemia (Hg <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis		Max dose of 1.75 mg/kg every 3 weeks for myelodysplastic syndromes	• Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure <u>Ongoing Monitoring</u> • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 weeks) • Hemoglobin level • Blood pressure

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
7. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/21 (SF); 8/20 (SS); 6/20; 2/20
Implementation: TBD; 11/1/20; 9/1/20; 7/1/20

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
margetuximab-cmkb	MARGENZA
naxitamab-gqgk	DANYELZA
relugolix	ORGOVYZ

Recommendation:

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

Appendix 1. Proposed Prior Authorization Criteria

Oncology Agents

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

Length of Authorization:

- Up to 1 year

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

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org

- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #6
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

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

Table 1. Oncology agents which apply to this policy (Updated 1/04/2020)

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

Generic Name	Brand Name
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
alpelisib	PIQRAY

apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
belinostat	BELEODAQ
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	BENDEKA
bendamustine HCl	TREANDA
binimetinib	MEKTOVI
belantamab mafodotin-blmf	BLENREP
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI

everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idelalisib	ZYDELIG
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gggk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
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

enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sonidegib phosphate	ODOMZO
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tisagenlecleucel	KYMRIAH
trabectedin	YONDELIS

polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-pkrb	HERZUMA
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-qyyp	TRAZIMERA
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trifluridine/tipiracil HCl	LONSURF
tucatinib	TUKYSA
vandetanib	CAPRELSA
vandetanib	VANDETANIB
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
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Anticoagulants

Date of Review: February 2021

Date of Last Review: November 2019
Literature Search: 09/01/19 – 01/04/20

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

Conclusions:

- There were five systematic reviews and meta-analyses, four new guidelines and two randomized controlled trials (RCTs) identified since the last review.
- Results from a 2020 Cochrane review demonstrated moderate evidence of an increased risk of stroke in patients treated with rivaroxaban compared to vitamin K antagonists (VKAs) in adult patients with antiphospholipid syndrome (APS), 14 versus 0 (relative risk [RR] of 14.13; 95% confidence interval [CI], 1.87 to 106.81).[1] Confidence intervals suggest imprecision most likely due the low number of events. There was no difference between groups in risk of thromboembolic events. The incidence in major bleeding was similar between groups (RR 1.10; 95% CI, 0.45 to 2.68) based on moderate evidence.
- Patients with no history of thromboembolism and undergoing knee arthroscopy (KA) were included in a Cochrane review.[2] In short term studies (30 days to 3 months), there was moderate evidence of no difference between control (no treatment) and low-molecular weight heparin (LMWH) for the outcomes of pulmonary embolism (PE) and there was also no conclusive evidence of differences between adverse events.[2] Very low quality evidence found no difference between LMWH and controls for symptomatic and asymptomatic deep vein thrombosis (DVT).
- Primary venous thromboembolism (VTE) prophylaxis in adult ambulatory patients with cancer found high strength of evidence that LMWH was more effective at decreasing the risk of any VTE compared to no treatment with moderate evidence of an increased risk of clinically relevant bleeding and major bleeding. There was moderate evidence that all DVT (symptomatic and asymptomatic) rates were decreased with non-vitamin K oral anticoagulants (NOACs) compared to no treatment; reductions in symptomatic DVT, symptomatic PE and VTE with NOACs compared to placebo were based on low strength of evidence. There was moderate evidence of increased clinically relevant bleeding and major bleeding in patients treated with NOACs.
- A Cochrane review found no differences between NOACs and VKAs in death from cardiovascular (CV) causes, myocardial infarction (MI), stroke, death from any cause and stent thrombosis in trials lasting 6 months to 2.2 years, based on very-low to moderate quality of evidence. Risk of major bleeding was less with dabigatran (low dose) compared to VKAs (RR 0.38; 95% CI, 0.21 to 0.70) (moderate quality evidence). All other NOAC comparisons to VKA found no substantial differences in major bleeding between groups.[3]
- High quality evidence from a Cochrane review on management of distal DVTs found VKAs to prevent more VTEs compared to placebo and treatment for 3 or more months was more effective in VTE reduction compared to 6 weeks of treatment.[4]
- Updated guidance from the National Institute for Health and Care Excellence (NICE) on venous thromboembolism and American Hematology Society (AHS) on the management of VTE were updated in 2020 and support our current policy.[5,6] The American Heart Association, American College of Cardiology and Heart Rhythm Society (AHA/ACC/HRS) guideline on the management of patients with atrial fibrillation (AF) also supports current policy.[7] Lastly, an update from the American Society of Clinical Oncology (ASCO) aligns with current policy.[8]

Author: Kathy Sentena, PharmD

- There were several Food and Drug Administration (FDA) safety updates, including the warning of an increased risk of thrombosis in patients with triple positive antiphospholipid syndrome with NOACs and use is not recommended.

Recommendations:
- No changes to the preferred drug list (PDL) are warranted based on the evidence identified since the last review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The anticoagulant class was last reviewed in November of 2019. New evidence for the treatment of VTE and atrial fibrillation (AF) was presented. No changes were made to the PDL based on clinical evidence or after comparative cost consideration in executive session.
- All anticoagulants are designated as preferred with the exception of: betrixaban, dalteparin, enoxaparin ampules, and fondaparinux.
- There is 100% utilization of preferred products for the anticoagulant class based on the most recent quarter data. There is higher NOAC utilization compared to warfarin.

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

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

New Systematic Reviews:

<u>Cochrane – Antiplatelet and Anticoagulant Agents for the Secondary Prevention of Stroke and Other Thromboembolic Events in People with Antiphospholipid Syndrome</u>
A 2020 Cochrane review evaluated the use of antiplatelets or anticoagulants, alone or in combination, in patients with APS for secondary prevention of thrombosis, in particular ischemic stroke.[1] There were 8 studies that met inclusion criteria which enrolled a total of 811 patients. The average age of patients were 36-50 years. Drugs included rivaroxaban 15-20 mg/day, aspirin (100 mg/day) and warfarin (standard-dose [INR 2.0 to 3.0] and high-dose (INR 3.1 to 4.0]).[1] The outcomes of interest were thromboembolic events, stroke, death and major bleeding.

Three trials compared standard dose VKA (INR 2.0-3.0) to rivaroxaban over a period of 7 months to 35.4 months.[1] There was no difference in the incidence of thrombotic events: VKAs 28 per 1000 patients compared to 115 per 1000 for patients treated with rivaroxaban (RR 4.08; 95% CI, 0.48 to 34.79) based on moderate evidence, which was downgraded due to imprecision.[1] Large confidence intervals suggests imprecision and uncertainty in the findings. The incidence

of major bleeding was similar between groups, 42 per 1000 for VKAs and 47 per 1000 patients taking rivaroxaban (RR 1.10; 95% CI, 0.45 to 2.68) (moderate quality evidence).[1] There was moderate quality of evidence that all-cause mortality rates were 19 per 1000 patients treated with VKAs and 28 per 1000 patients treated with rivaroxaban (RR 1.45; 95% CI, 0.44 to 4.78). There were 14 strokes with rivaroxaban compared to none in patients treated with VKA, (RR of 14.13; 95% CI, 1.87 to 106.81).[1] Confidence intervals suggest imprecision most likely due the low number of events (moderate quality of evidence). There was moderate quality of evidence of no difference in clinically relevant non-major bleeding between VKAs and rivaroxaban, 47 per 1000 and 80 per 1000 (RR 1.70; 95% CI, 0.69 to 4.19).[1]

There were 2 studies (n=223) that compared high-dose VKA compared to standard-dose VKA. All evidence was graded as low quality.[1] There was no statistically significant differences between groups for the following outcomes: any thromboembolic events, major bleeding, all-cause mortality, or stroke. There were concerns of incomplete outcome reporting and selective outcome reporting in both studies and one study was underpowered due to poor recruitment, resulting in early termination. The risk for any bleeding was higher with high-dose VKA compared to standard-dose VKA (hazard ratio [HR] 2.03; 95% CI, 1.12 to 3.68).[1]

One RCT (n=82) compared standard-dose VKA plus a single antiplatelet agent versus standard-dose VKA and found low to very low quality evidence for all outcomes studied.[1] There was a difference in the number of thrombotic events favoring standard-dose VKA compared to standard-dose VKA plus an antiplatelet agent, 184 per 1000 patients treated compared to 394 per 1000 patients, respectively (RR 2.14; 95% CI, 1.04 to 4.43).[1] There was no statistically significant differences demonstrated between the groups for all other outcomes studied. There was no allocation concealment in the trial, which downgraded the evidence. There was also imprecision due to the low number of events.

<u>Cochrane – Interventions for Preventing Venous Thromboembolism in Adults Undergoing Knee Arthroscopy</u>
Cochrane updated their 2007 review on VTE prevention in patients undergoing KA in 2020.[2] A literature search ending in August 2019 identified four new studies, bringing the total to 8 studies (n=3818). All studies were at low or unclear risk of bias. Patients were adults with no history of thromboembolism who were scheduled for KA. Drug treatments included: aspirin, LMWH, rivaroxaban 10 mg and aspirin.[2] All comparisons involved only one study with the exception of LMWH, in which there were 5. Results are limited to patients with no history of thrombosis due to exclusion of secondary prevention patients and patients with risk factors.

There were no deaths in any of the groups and the incidence of PE was low across all studies, which could be attributed to short durations of follow-up lasting from 30 days to 3 months.[2] In studies of LMWH compared to control (no prophylactic treatment) there was no difference in PE (assessed with CT arteriography) with a RR of 1.81 (95% CI, 0.49 to 6.65) (moderate quality evidence).[2] Symptomatic and asymptomatic DVT rates were not different between groups based on low to very low quality of evidence. Evidence was downgraded due to imprecision and indirectness. There was moderate quality evidence that the incidence of all adverse events, was not different between those randomized to control and those treated with LMWH, 13 per 1000 and 24 per 1000, respectively (RR 1.85; 95% CI, 0.95 to 3.59).[2] Major bleeding rates were 1 per 1000 for both control and LMWH (RR 0.98; 95% CI, 0.06 to 15.72) based on moderate quality evidence. Minor bleeding rates were also similar between groups (RR 1.79; 95% CI, 0.84 to 3.84).[2] There was imprecision in the results for adverse events and minor and major bleeding rates.

A study comparing rivaroxaban to placebo found moderate strength of evidence that the incidence in DVT was not clinically different between the groups (RR 0.16; 95% CI, 0.02 to 1.29).[2] Evidence was insufficient for data on risk of PE. There were no differences found between minor (RR 0.63; 95% CI, 0.18 to 2.19) and major bleeding rates (none reported in either group).

There was one study comparing aspirin to control; however, there were no events for PE, symptomatic or asymptomatic DVT in either group to inform treatment comparisons.[2]

Cochrane – Primary Prophylaxis for Venous Thromboembolism In Ambulatory Cancer Patients Receiving Chemotherapy

Primary prophylaxis for ambulatory patients with cancer and receiving chemotherapy were the focus of a 2020 Cochrane review, which updates a 2012 version.[9] Active treatment was compared to placebo, or no treatment, in 6 (n=3326) newly identified trials. Participants were adult patients with locally advanced or metastatic cancer. Imprecision and high risk of bias resulted in downgrading the evidence for some outcomes.

The use of NOACs compared to placebo or no thromboprophylaxis was studied in 3 trials in high-risk populations with a median follow-up of 6 months. There was low quality evidence that NOACs may decrease the incidence of VTE (RR 0.42; 95% CI, 0.18 to 1.06), symptomatic PE (RR 0.38; 95% CI, 0.10 to 1.47) and symptomatic DVT (RR 0.51; 95% CI, 0.21 to 1.22).[9] Moderate quality evidence reported an increase in major bleeding with NOACs compared to placebo, 32 per 1000 versus 18 per 1000 patients treated (RR 1.74; 95% CI, 0.82 to 3.68).[9] The incidence of any DVT was lower with NOACs compared to placebo, 52 per 1000 patients treated versus 95 per 1000 patients treated (RR 0.55; 95% CI, 0.34 to 0.90) (moderate quality evidence).[9] There was moderate quality evidence that the risk of clinically relevant bleeding was higher with NOACs compared to placebo, 52 per 1000 patients treated versus 32 per 1000 patients treated (RR 1.61; 95% CI, 0.82 to 3.15).[9]

There were 15 studies that evaluated the use of LMWH compared to no thromboprophylaxis. The evidence ranged from low to high with an average follow-up of 10 months (**Table 1**).[9] While there was some variability in dosing strategies of LMWH, results were consistent, so there was no downgrading of the evidence due to dosing.

Table 1. LMWH Compared to No Thromboprophylaxis in for Primary Prevention of VTE in Ambulatory Cancer Patients at High-Risk[9]

Outcomes	Results	Strength of Evidence	Comments
Symptomatic VTE	RR 0.62; 95% CI, 0.46 to 0.83	High	There is high confidence that LMWH decreases the risk of VTE compared to no treatment
Major Bleeding	RR 1.63; 95% CI, 1.12 to 2.35	Moderate	There is high probability that LMWH increases the risk of major bleeding compared to no treatment
Symptomatic PE	RR 0.60; 95% CI, 0.42 to 0.88	Moderate	There is high probability that the risk of symptomatic PE is reduced with LMWH compared to no treatment
Symptomatic DVT	RR 0.48; 95% CI, 0.35 to 0.67	High	There is high confidence that LMWH decreases the risk of symptomatic DVE compared to no treatment
Any VTE	RR 0.57; 95% CI, 0.46 to 0.71	High	There is high confidence that the LMWH decreases the risk of any VTE compared to no treatment
1-year overall Mortality	RR 0.94: 95% CI, 0.83 to 1.07	Low	There is evidence that LMWH may decrease the incidence of death compared to no treatment
Clinically Relevant Bleeding	RR 3.40; 95% CI, 1.20 to 9.63	Moderate	There is high probability that LMWH increases the incidence of clinically relevant bleeding compared to no treatment

LMWH was compared to aspirin in 2 RCTs with a median follow-up of 18.5 months studied in patients with multiple myeloma.[9] There was moderate quality evidence that symptomatic VTE rates were reduced with LMWH with an incidence of 20 per 1000 patients versus 39 per 1000 patients treated with aspirin (RR 0.51; 95% CI, 0.22 to 1.17).[9] There was moderate quality evidence that LMWH reduces the risk of symptomatic PE compared to aspirin resulting in 15 per 1000 fewer events (RR 0.13; 95% CI, 0.02 to 1.03). The risk of symptomatic DVT with LMWH was reduced compared to aspirin by 5 per 1000 fewer events (RR 0.81; 95% CI, 0.32 to 2.04). The evidence for major bleeding was of low quality with an incidence for LMWH of 1 per 1000 treated compared to 7 per 1000 patients treated for aspirin.[9]

LMWH was compared to VKA in one RCT in patients with multiple myeloma patients at high-risk of VTE. There was high quality evidence that LMWH reduced the risk of symptomatic VTE compared to aspirin, 55 per 1000 fewer events (RR 0.33; 95% CI, 0.14 to 0.83).[9] LMWH probably decreases the incidence of symptomatic DVT compared to VKA, 27 per 1000 versus 64 per 1000 (RR 0.43; 95% CI, 0.17 to 1.10). There was low quality evidence that symptomatic PE rates were reduced more with LMWH compared to VKA with 16 per 1000 fewer events (RR 0.11; 95% CI, 0.01 to 2.06); however, results were not statistically significant.[9]

One randomized controlled trial compared to VKA to aspirin in patients with multiple myeloma at intermediate-risk of VTE. VKA probably increases the risk of VTE compared to aspirin with an incidence of 82 per 1000 compared to 55 per 1000 patients treated with aspirin (RR 1.50; 95% CI, 0.74 to 3.04); however, results are not statistically significant and associated with some uncertainty (moderate quality evidence).[9] There was moderate quality evidence that the incidence of symptomatic PE with VKAs is similar to aspirin with an incidence of 18 per 1000 patients treated in both groups (RR 1.00; 95% CI, 0.25 to 3.95). Symptomatic DVT incidence was higher with VKAs compared to ASA with 27 per 1000 patients treated (RR 1.75; 95% CI, 0.75 to 4.09); however, differences were not statistically significant (moderate quality evidence).[9]

The evidence for LMWH compared to active control and for VKAs compared to placebo was of low quality and no conclusions on efficacy could be determined. There was very low strength of evidence for outcomes comparing antithrombin versus no thromboprophylaxis.

<u>Cochrane – Non-vitamin K Antagonist Oral Anticoagulants (NOACs) Post Percutaneous Coronary Intervention (PCI)</u>
A recent Cochrane review studied the evidence for the use of NOACs compared to VKAs in patients post-PCI with a need for anticoagulation.[3] Results were presented as a direct evidence comparison and as a network meta-analysis (NMA). There were 5 trials with a total of 8373 participants. There were 2 studies comparing apixaban to a VKA, 2 studies comparing rivaroxaban (2.5 mg [low dose] and 10 mg [high-dose]) to a VKA and one study comparing dabigatran (110 mg [low-dose] and 150 mg [high-dose] to a VKA. Follow-up ranged from 6 months to 2.2 years.[3]

Evidence from the apixaban trials demonstrated moderate quality of evidence that death from CV causes was similar between apixaban and VKA with one more death per 1000 patients treated with apixaban compared to VKAs (direct: RR 1.06; 95% CI, 0.74 to 1.51 and NMA: 1.06; 95% CI, 0.41 to 2.275).[3] The evidence comparing low dose rivaroxaban to VKAs and high-dose rivaroxaban to VKAs was very low quality for the outcome of death from CV causes and found no differences between groups.

There was moderate quality evidence that the incidence of MI was 30 fewer with apixaban compared to VKAs; same relative risk for both direct and NMA (0.89; 95% CI, 0.65 to 1.20); however, not statistically or clinically different.[3] The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was of low to very-low quality with no statistically significant findings. The evidence for the incidence of stroke was considered low to very low quality for all comparisons.

For the outcome of major bleeding, as defined by the Thrombolysis In Myocardial Infarction (TIMI) criteria, 7 fewer per 1000 patients experienced an episode if treated with apixaban compared to those treated with VKA (direct and NMA: RR 0.82 (95% CI, 0.55 to 1.21); which suggests no clinically significant differences and is not statistically different (moderate quality evidence).[3] There was moderate quality evidence that low-dose dabigatran caused 23 fewer per 1000 cases of major bleeding compared to VKAs (direct and NMA: RR 0.38; 95% CI, 0.21 to 0.70).[3] There was low to very low quality evidence for major bleeding outcomes for rivaroxaban (low and high dose) and dabigatran. Evidence was downgraded due to imprecision.

There was moderate quality evidence for the outcome of death from any cause that apixaban was associated with 8 more deaths per 1000 patients treated compared to VKAs, which was not statistically significant (direct and NMA: RR 1.18; 95% CI, 0.74 to 1.87).[3] The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was of low quality and demonstrated no clinically meaningful differences.

There was a non-significant reduction in stent thrombosis in patients treated with apixaban compared to VKAs based on moderate quality evidence, 6 per 1000 versus 8 per 1000 (direct: RR 0.78; 95% CI, 0.39 to 1.56 and NMA: RR 0.78; 95% CI, 0.39 to 1.56).[3] The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was considered low quality.

Cochrane – Treatment of Distal Deep Vein Thrombosis

A 2020 Cochrane review evaluated different treatments for people with distal (below the knee) DVT.[4] Eight trials (n=1239) were included, five of which compared anticoagulants (e.g., VKAs) to placebo for 3 months and three trials evaluated the use of anticoagulants for different time periods.

There was high quality evidence that VKAs prevented more recurrent VTEs compared to placebo, 31 per 1000 versus 91 per 1000 (RR 0.34: 95% CI, 0.15 to 0.77).[4] There were a small number of events but a large treatment effect maintaining the high certainty of results. The risk of recurrent DVT with use of VKAs was 20 per 1000 compared to 79 per 1000 on placebo (RR 0.25; 95% CI, 0.10 to 0.67) (high quality of evidence).[4] There was high quality evidence that clinically relevant non-major bleeding was increased with VKAs compared to placebo by 43 more events per 1000 (RR 3.34; 95% CI, 1.07 to 10.46); however, wide confidence intervals suggest uncertainty in the findings.[4] The evidence for the outcomes of PE, major bleeding and overall mortality were of low certainty and not statistically significant between groups.

Three trials, with up to 24 months follow-up, evaluated the effect of anticoagulation for 3 months or more compared to anticoagulation for 6 weeks in patients with distal DVT. There was high quality evidence that risk of recurrent VTE was 57 per 1000 for patients treated with 3 months or more of anticoagulation and 135 per 1000 for those treated with 6 weeks (RR 0.42; 95% CI, 0.26 to 0.68).[4] The risk of recurrent DVT was reduced in patients treated with 3 months or longer compared to 6 weeks of therapy (RR 0.32; 95% CI, 0.16 to 0.64) (high quality evidence).[4] The evidence for major bleeding, PE, and clinically relevant non-major bleeding was of low quality with large confidence intervals and uncertainty in conclusions. Overall mortality and mortality related to PE were not reported.

After review, 50 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). [10-60]

New Guidelines:
High Quality Guidelines:

NICE – Venous Thromboembolic Diseases

NICE updated their 2015 guidance on the diagnosis and recommendations for treatment of thromboembolic diseases.[5] Specific treatment recommendations are presented in **Table 2**. Treatment of DVT is focused on the diagnosis of proximal DVT as distal DVT is associated with less risk. Duration of anticoagulation treatment should be for at least 3 months for individuals with confirmed proximal DVT or PE. Patients with active cancer, and confirmed proximal DVT or PE, should be offered anticoagulation treatment for 3 to 6 months, dependent upon clinical need.[5] There is insufficient evidence comparing inpatient versus outpatient treatment of patients at low-risk and have a confirmed PE and there is no evidence to suggest outpatient treatment is less effective or less safe. NICE recommends outpatient treatment for these patients with intensive monitoring and follow-up. There is insufficient evidence on interim anticoagulation treatment but recommend treatment if diagnostic tests are delayed for than 4 hours. Long-term anticoagulation, treatment beyond 3 months (6 months for patients with active cancer) was deemed most appropriate in patients with an unprovoked DVT or PE and at low risk of bleeding.

Table 2. NICE Recommendations for the Treatment of Thromboembolic Diseases[5]

Indication	Recommendation
Proximal DVT or PE with no relevant comorbidities or significant clinical features	• Apixaban • Rivaroxaban • If neither of the above are suitable offer the following: - LMWH for at least 5 days followed by dabigatran or edoxaban OR - LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own • UFH should only be offered to patients with renal impairment or renal failure or an increased risk of bleeding
Proximal DVT or PE with renal impairment (CrCl 15 ml/min and 50 ml/min)	• Apixaban • Rivaroxaban • LMWH for at least 5 days followed by - Edoxaban - Dabigatran if estimated CrCL is 30 ml/min or above • LMWH or UFH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with renal failure (CrCl of less than 15 ml/min)	• LMWH • UFH • LMWH or UFH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with triple positive antiphospholipid syndrome	• LMWH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with active cancer	• Treatment with an anticoagulant for 3-6 months

	• Consider a NOAC • If a NOAC is unsuitable consider LMWH alone or LMWH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings
Treatment failure	• Increase dose of anticoagulant or change to an anticoagulant with a different mode of action
Long-term anticoagulation for secondary prevention	• Offer continued treatment with current anticoagulant if long-term anticoagulation is deemed appropriate OR • Consider changing patient to apixaban if they are being treated with a NOAC other than apixaban • If patients denies long-term anticoagulation treatment offer aspirin 75 mg daily or 150 mg daily
Proximal DVT or PE in patients with extremes of body weight	• Recommend anticoagulation with regular monitoring of therapeutic levels for those who weigh less than 50 kg or more than 120 kg to ensure effective anticoagulation (no specific drug recommendations were provided)
Abbreviations: CrCl – creatinine clearance; DVT- deep vein thrombosis; LMWH – low-molecular-weight heparin; NOACs – non-vitamin K oral anticoagulants; PE – pulmonary embolism; UFH – unfractionated heparin; VKA – vitamin K antagonist	

American Society of Hematology – Management of VTE: Treatment of DVT and PE

In 2020 the ASH updated guidance on the management of VTE, including the treatment recommendations for DVT and PE.[6] The guideline was deemed good quality according to the AGREE II tool. Recommendations were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and assigned a "strong", many patients would opt for the recommended treatment or action, or "conditional recommendation", the majority of patients would want treatment or action but many would not. There are 17 recommendation pertaining to the use of anticoagulants (**Table 3**).

Table 3. Recommendations for the Management of VTE from the ASH[6]

Condition	Recommendation	Evidence	Strength of Recommendation
Patients with DVT and/or PE*	NOAC use over VKAS	Moderate	Conditional
Patients with DVT and/or PE	No preference in NOAC	Very low	Conditional
Patients with proximal DVT	Anticoagulation therapy alone over thrombolytic therapy and anticoagulation therapy	Low	Conditional
Patients with PE and hemodynamic compromise	Thrombolytic therapy followed by anticoagulation	Low	Strong
Patients with PE and echocardiographic and/or biomarkers compatible with right ventricular dysfunction but without hemodynamic compromise	Anticoagulation alone over use of thrombolysis in additional to anticoagulation	Low	Conditional
Patients with proximal DVT and significant preexisting cardiopulmonary disease as well as patients with PE and hemodynamic compromise	Anticoagulation alone versus anticoagulation plus insertion of an inferior vena cava (IVC) filter	Low	Conditional
Primary treatment of DVT and/or PE (due to TIA, chronic risk factor, or unprovoked)	Shorter courses of anticoagulation for primary treatment (3-6 months) versus longer courses (6-12 months)	Moderate	Conditional

Patients with chronic risk factors who finish primary treatment	Indefinite antithrombotic therapy	Moderate	Conditional
Patients with unprovoked DVT and/or PE who finish primary treatment	Indefinite antithrombotic therapy	Moderate	Conditional
Patients with DVT and/or PE who finish primary treatment and will continue to receive secondary prevention	Anticoagulation is recommended over aspirin	Moderate	Conditional
Patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention	Standard dose NOAC or a lower-dose DOAC (e.g., rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily)	Moderate	Conditional
For patients with breakthrough DVT and/or PE during therapeutic VKA therapy	Switch to LMWH over a NOAC†	Very low	Conditional
For patients who develop DVT and/or PE provoked by a transient risk and have a history of previous unprovoked VTE or VTE provoked by a chronic risk factor	Indefinite antithrombotic therapy over stopping anticoagulation after completing primary treatment	Moderate	Conditional
Patients who develop DVT and/or PE provoked by a transient risk factor and have a history of previous VTE also provoke by a transient risk factor	Discontinue anticoagulation after completion of primary treatment	Moderate	Conditional
For patients with a recurrent unprovoked DVT and/or PE provoked by a transient risk factor	Indefinite antithrombotic therapy after completion of primary treatment	Moderate	Strong
For patients who develop DVT and/or PE with stable CVD who initiate anticoagulation and were previously taking aspirin for CV risk modification	Suspend aspirin over continuing it for the duration of anticoagulation treatment	Very low	Conditional
Key: * Does not apply to patients with renal insufficiency (CrCl <30 ml/min), moderate to severe liver disease, or antiphospholipid syndrome; † Does not apply to patients with subtherapeutic INRs or those whom a NOAC may be a reasonable option Abbreviations: CrCl – creatinine clearance; CV – cardiovascular; CVD – cardiovascular disease; DVT- deep vein thrombosis; LMWH – low-molecular-weight heparin; NOACs – non-vitamin K oral anticoagulants; PE – pulmonary embolism; TIA – transient ischemic attack; VKA – vitamin K antagonist			

AHA/ACC/HRS – Management of Patients with Atrial Fibrillation

The collaboration of three societies produced a 2019 guideline on the management of atrial fibrillation.[7] The methods for guideline development and grading of the evidence, resulting in strength of guideline recommendation, are clearly described and presented in **Table 4**. This guideline serves as an update to the 2014 guidance.

Table 4. AHA/ACC/HRS Class Recommendation Definitions and Levels of Evidence (abbreviated)[7]

CLASS (STRENGTH) OF RECOMMENDATION	
Class I (Strong) Benefit >>>Risk	• Is recommended • Treatment A is recommended in preference to treatment B
Class IIa (Moderate) Benefit >>Risk	• Is reasonable • Treatment A is probably recommended in preference to treatment B
Class IIb (Weak) Benefit ≥Risk	• May/might be reasonable • Effectiveness is unknown or not well established
Class III: No benefit (Moderate) Benefit = Risk	• Is not recommended
Class III: Harm (Strong) Risk>Benefit	• Potentially harmful
LEVEL (QUALITY OF EVIDENCE)	
Level A	• High-quality evidence from more than 1 RCT • Meta-analysis of high-quality trials • One or more RCTs corroborated by high-quality registry studies
Level B-R (randomized)	• Moderate-quality evidence from one or more RCT • Meta-analysis of moderate quality trials
Level B-NR (not randomized)	• Moderate quality of evidence from 1 or more well-designed RCT, observational or registry studies • Meta-analysis of such studies
Level C-LD (limited data)	• Randomized or non-randomized observational or registry studies with limitations of design or execution • Meta-analysis of such studies • Physiological or mechanistic studies in human subjects
Level C-EO	• Consensus of expert opinion based on clinical experience

Pharmacological recommendations as they pertain to AF will be presented (**Table 5**). An update to the guideline is the use of the $CHAD_2DS_2$-VASc score, which is more precise. NOACs are recommended over warfarin due to evidence of being non-inferior or superior to warfarin in clinical trials with lower risks of bleeding.

Table 5. Recommendations from the AHA/ACC/HRS on Pharmacological Treatments for Patients with Atrial Fibrillation[7]

Condition	Recommendation	Class of Recommendation	Level of Evidence
For patients with AF and an elevated $CHAD_2DS_2$-VASc score or 2 or greater in women	• Oral anticoagulants are recommended: - Warfarin - Dabigatran - Rivaroxaban	I for all	 A B B

	- Apixaban - Edoxaban		B B-R
In NOAC-eligible patients with AF*	• NOACs (see above) are recommended over warfarin (except those with mitral stenosis or a mechanical heart valve)	I	A
In patients treated with warfarin	• INR should be determined weekly upon initiation and at least monthly when INR is stable	I	A
Patients with AF and mechanical heart valves	• Warfarin is recommended	I	B
Anticoagulant therapy selection	• Should be based on risk of thromboembolism, irrespective of AF pattern	I	B
In patients prescribed NOACs	• Renal function should be evaluated before initiation and at least annually	I	B-NR
In patients who anticoagulants are recommended	• Absolute risks and relative risk of stroke and bleeding risks should be discussed with the patient	I	C
For patients with atrial flutter	• The same anticoagulant recommendations apply as those with patients with AF	I	C
Patients on anticoagulant therapy for stroke	• Periodic assessment of stroke and bleeding risk with need and choice of anticoagulant should be done	I	C
Patients who are unable to obtain a therapeutic INR*	• NOAC is recommended	I	C-EO
For patients with AF and an elevated $CHAD_2DS_2$-VASc score of 0 in men or 1 in women*	• Anticoagulant therapy can be omitted	IIa	B
For patients with AF and an elevated $CHAD_2DS_2$-VASc score of 2 or greater in men and 3 or greater in women and have end-stage chronic kidney disease (CrCl <15 mL/min) or are on dialysis	• May be reasonable to prescribe warfarin (INR 2.0-3.0) or apixaban	IIb	B-NR
For patients with AF and an elevated $CHAD_2DS_2$-VASc score with moderate-to-severe CKD*	• Treatment with a reduced dose of NOAC may be considered	IIb	B-R
For patients with AF and an elevated $CHAD_2DS_2$-VASc score of 1 in men or 2 in women	• Prescribing an oral anticoagulant may be considered	IIb	C-LD
For patients with AF and end-stage CKD or on dialysis	• Rivaroxaban, dabigatran or edoxaban are not recommended	III	C-EO
In patients with AF and a mechanical heart valve	• Dabigatran should not be used	III	B-R
Abbreviations: AF – atrial fibrillation; $CHAD_2DS_2$-VASc – congestive heart failure, hypertension, age 75 years or older (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; CKD – chronic kidney disease; CrCl – creatinine clearance; INR – international normalized ratio; NOACs – non-vitamin K oral anticoagulants. Key: * Except with moderate-to severe mitral stenosis or a mechanical heart valve			

ASCO – VTE Prophylaxis and Treatment in Patients with Cancer

Guidance from the ASCO was updated in a 2020 guideline for the prophylaxis and treatment of VTE in patients with cancer.[8] The guideline met criteria inclusion outlined in the Drug Use Research and Management methods. Evidence was graded from "insufficient to high" and recommendations were given a "weak to strong" designation. Recommendations pertaining to anticoagulant use are presented in **Table 6**. Recommendations for treatment of incidental PE and DVT are the same as symptomatic VTE.

Table 6. ASCO Recommendations for the Use of Anticoagulants for VTE Prophylaxis and Treatment in Patients with Cancer[8]

Condition	Recommendation	Evidence Quality	Strength of Recommendation
Hospitalized patients with active malignancy and acute medical illness or reduced mobility	Pharmacological thromboprophylaxis in absence of bleeding or other contraindications should be offered	Intermediate	Moderate
Hospitalized patients who have active malignancy without additional risk factors	Pharmacological thromboprophylaxis in absence of bleeding or other contraindications may be offered	Low	Moderate
Patients admitted for the sole purpose of minor procedures or chemotherapy infusion or stem-cell/bone-marrow transplantation	Routine thromboprophylaxis should not be offered	Insufficient	Moderate
Outpatient, ambulatory patients with cancer receiving systemic chemotherapy	Routine thromboprophylaxis should not be offered	Intermediate to high	Strong
High-risk outpatients with cancer*	May be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH if there are no significant risk factors for bleeding or drug interactions	Intermediate to high	Moderate
Patients with multiple myeloma receiving thalidomide or lenalidomide-based regimens with chemotherapy and/or dexamethasone	Pharmacological thromboprophylaxis should be offered with aspirin or LMWH in lower-risk patients and LMWH for higher-risk patients	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be offered with UFH or LMWH unless contraindicated (including bleeding)	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be started preoperatively	Intermediate	Moderate

Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis and mechanical prophylaxis may improve efficacy	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be continued for a least 7 to 10 days and up to 4 weeks	High	Strong
Patients with cancer with established VTE	Initial anticoagulation may involve LMWH, UFH, fondaparinux or rivaroxaban For patients initiating parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days in patients with a newly diagnosed VTE without severe renal impairment	High	Strong
Patients with cancer with established VTE on long-term anticoagulation	LMWH, rivaroxaban, or edoxaban for at least 6 months are preferred over VKAs VKAs may be used if LMWH or NOACs are not assessible	High	Strong
Patients with cancer (metastatic disease or those receiving chemotherapy) with established VTE on long-term anticoagulation	Anticoagulation beyond 6 months should be offered and assessed on an intermittent basis to ensure a favorable risk-benefit profile	Low	Weak to moderate (consensus recommendation)
Patients with primary or metastatic CNS malignancies and established VTE	Anticoagulation as previously described should be offered; however, uncertainties on choice of agent remain	Low	Moderate
Patients with cancer without established VTE	Anticoagulant use is not recommended	High	Strong
Abbreviations: CNS- central nervous system; LMWH – low-molecular weight heparin; NOACs – non-vitamin K oral anticoagulants; UFU – unfractionated heparin; VKAs – vitamin-K antagonists; VTE – venous thromboembolism Key: * Khorana score of 2 or higher prior to starting a new systemic chemotherapy			

After review, one guideline was excluded due to poor quality.[61]

New Formulations:
None identified

New Indications:

Rivaroxaban (Xarelto) – In October 2019 rivaroxaban was approved for use in for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications in patients not at high risk of bleeding.[62] Evidence for the new indication for rivaroxaban was from the MAGELLAN study, a multicenter, double-blind, parallel-group RCT which compared rivaroxaban 10 mg daily for 35 days to enoxaparin 40 mg daily for 10 days. Patients were at least 40 years of age with additional risk factors for VTE. The primary endpoint (composite of asymptomatic proximal DVT in lower extremity, symptomatic non-fatal PE, and death related to VTE) measured at day 35 occurred in 4.4% of patients receiving rivaroxaban and 5.7% of patients treated with enoxaparin (RR 0.77; 95% CI, 0.62 to 0.96). Results were not available for 25% of patients due to lack of untrasonographic assessment (13.5%), inadequate assessment (8.1%) or lack of intake of study medication (1.3%).

New FDA Safety Alerts:

Table 7. 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)
Apixaban[63]	Eliquis	11/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Betrixaban[64]	Bevyxxa	08/2020	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Dabigatran[65]	Pradaxa	11/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Edoxaban[66]	Savaysa	04/2020	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Rivaroxaban[62]	Xarelto	10/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Rivaroxaban[67]	Xarelto	11/2019	Dosage and Administration	Updates to the dosing in patient with renal impairment
Rivaroxaban[68]	Xarelto	03/2020	Warnings and Precautions	Not recommended for use in patients with prosthetic heart valves

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
apixaban	ELIQUIS	TAB DS PK	PO	Y
apixaban	ELIQUIS	TABLET	PO	Y
dabigatran etexilate mesylate	PRADAXA	CAPSULE	PO	Y
dalteparin sodium,porcine	FRAGMIN	SYRINGE	SQ	Y
edoxaban tosylate	SAVAYSA	TABLET	PO	Y
enoxaparin sodium	ENOXAPARIN SODIUM	SYRINGE	SQ	Y
enoxaparin sodium	LOVENOX	SYRINGE	SQ	Y
enoxaparin sodium	ENOXAPARIN SODIUM	VIAL	SQ	Y
enoxaparin sodium	LOVENOX	VIAL	SQ	Y
rivaroxaban	XARELTO	TAB DS PK	PO	Y
rivaroxaban	XARELTO	TABLET	PO	Y
warfarin sodium	COUMADIN	TABLET	PO	Y
warfarin sodium	JANTOVEN	TABLET	PO	Y
warfarin sodium	WARFARIN SODIUM	TABLET	PO	Y
betrixaban maleate	BEVYXXA	CAPSULE	PO	N
dalteparin sodium,porcine	FRAGMIN	VIAL	SQ	N
enoxaparin sodium	LOVENOX	AMPUL	SQ	N
fondaparinux sodium	ARIXTRA	SYRINGE	SQ	N
fondaparinux sodium	FONDAPARINUX SODIUM	SYRINGE	SQ	N

Appendix 2: New Comparative Clinical Trials

A total of 190 citations were manually reviewed from the initial literature search. After further review, 2 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 188 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Bonaca M, et al[69] (VOYAGER PAD)	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg Vs.	Patients 50 years or older with peripheral artery disease who had undergone revascularization	Composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes	Rivaroxaban 2.5 mg twice daily + aspirin: 508 (15.5%) Placebo + aspirin: 584 (17.8) HR 0.85 (95% CI, 0.76 to 0.96) P=0.009

Phase III, DB, PC, MC, RCT	Placebo + aspirin 100 mg Follow-up: 3 years	(n=6564)		
Dangas G, et al[70] (GALILEO) Phase III, OL, MC, RCT	Rivaroxaban 10 mg daily (+ Aspirin 75 – 100 mg for the first 3 months) Vs. Aspirin 75 – 100 mg (+ clopidogrel 75 mg for the first 3 months) Median follow-up: 17 months	Patients without and established indication for oral anticoagulation after successful transcatheter aortic-valve replacement (TAVR) (n=1654)	Composite of death or first thromboembolic event	Rivaroxaban: 105 Aspirin: 78 HR 1.35; 95% CI, 1.01 to 1.81 P=0.04

Abbreviations: DB – double-blind; MC – multi-center; OL – open label; PC – placebo controlled; RCT = randomized clinical trial; etc.

Appendix 3: Abstracts of Comparative Clinical Trials

Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc Bonaca, Rupert M Bauersachs, Sonia S Anand, E Sebastian Debus, Mark R Nehler, Manesh R Patel, Fabrizio Fanelli, Warren H Capell, Lihong Diao, Nicole Jaeger, Connie N Hess, Akos F Pap, John M Kittelson, Ivan Gudz, Lajos Mátyás, Dainis K Krievins, Rafael Diaz, Marianne Brodmann, Eva Muehlhofer, Lloyd P Haskell, Scott D Berkowitz, William R Hiatt

Abstract

Background: Patients with peripheral artery disease who have undergone lower-extremity revascularization are at high risk for major adverse limb and cardiovascular events. The efficacy and safety of rivaroxaban in this context are uncertain.

Methods: In a double-blind trial, patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification; major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) was a secondary safety outcome.

Results: A total of 6564 patients underwent randomization; 3286 were assigned to the rivaroxaban group, and 3278 were assigned to the placebo group. The primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan-Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P = 0.009). TIMI major bleeding occurred in 62 patients in the rivaroxaban group and in 44 patients in the placebo group (2.65% and 1.87%; hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P = 0.07). ISTH major bleeding occurred in 140 patients in the rivaroxaban group, as compared with 100 patients in the placebo group (5.94% and 4.06%; hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P = 0.007).

Conclusions: In patients with peripheral artery disease who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. (Funded by Bayer and Janssen Pharmaceuticals; VOYAGER PAD ClinicalTrials.gov number, NCT02504216.).

A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

George D Dangas, Jan G P Tijssen, Jochen Wöhrle, Lars Søndergaard, Martine Gilard, Helge Möllmann, Raj R Makkar, Howard C Herrmann, Gennaro Giustino, Stephan Baldus, Ole De Backer, Ana H C Guimarães, Lars Gullestad, Annapoorna Kini, Dirk von Lewinski, Michael Mack, Raúl Moreno, Ulrich Schäfer, Julia Seeger, Didier Tchétché, Karen Thomitzek, Marco Valgimigli, Pascal Vranckx, Robert C Welsh, Peter Wildgoose, Albert A Volkl, Ana Zazula, Ronald G M van Amsterdam, Roxana Mehran, Stephan Windecker, GALILEO Investigators

Abstract

Background: Whether the direct factor Xa inhibitor rivaroxaban can prevent thromboembolic events after transcatheter aortic-valve replacement (TAVR) is unclear.

Methods: We randomly assigned 1644 patients without an established indication for oral anticoagulation after successful TAVR to receive rivaroxaban at a dose of 10 mg daily (with aspirin at a dose of 75 to 100 mg daily for the first 3 months) (rivaroxaban group) or aspirin at a dose of 75 to 100 mg daily (with clopidogrel at a dose of 75 mg daily for the first 3 months) (antiplatelet group). The primary efficacy outcome was the composite of death or thromboembolic events. The primary safety outcome was major, disabling, or life-threatening bleeding. The trial was terminated prematurely by the data and safety monitoring board because of safety concerns.

Results: After a median of 17 months, death or a first thromboembolic event (intention-to-treat analysis) had occurred in 105 patients in the rivaroxaban group and in 78 patients in the antiplatelet group (incidence rates, 9.8 and 7.2 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.35; 95% confidence interval [CI], 1.01 to 1.81; P = 0.04). Major, disabling, or life-threatening bleeding (intention-to-treat analysis) had occurred in 46 and 31 patients, respectively (4.3 and 2.8 per 100 person-years; hazard ratio, 1.50; 95% CI, 0.95 to 2.37; P = 0.08). A total of 64 deaths occurred in the rivaroxaban group and 38 in the antiplatelet group (5.8 and 3.4 per 100 person-years, respectively; hazard ratio, 1.69; 95% CI, 1.13 to 2.53).

Conclusions: In patients without an established indication for oral anticoagulation after successful TAVR, a treatment strategy including rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy. (Funded by Bayer and Janssen Pharmaceuticals; GALILEO ClinicalTrials.gov number, NCT02556203.).

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to December 31, 2020
Search Strategy:

#	Searches	Results
1	apixaban.mp.	4039
2	dabigatran.mp. or Dabigatran/	5684
3	dalteparin.mp. or Dalteparin/	1359
4	edoxaban.mp.	1688
5	enoxaparin.mp. or Enoxaparin/	5542
6	rivaroxaban.mp. or Rivaroxaban/	6291
7	warfarin.mp. or Warfarin/	30958
8	betrixaban.mp.	191
9	fondaparinux.mp. or Fondaparinux/	2000
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	44098
11	limit 10 to (english language and humans and yr="2019 -Current")	2683
12	limit 11 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	190

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for anticoagulation
Intervention	Anticoagulants
Comparator	Placebo or active treatment comparisons
Outcomes	Incidence of venous thromboembolism, deep vein thrombosis, or pulmonary embolism; stroke, mortality, bleeding
Timing	Prophylaxis or treatment
Setting	Inpatient or outpatient

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Eligibility	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Total Members (FFS & Encounter)	980,226	981,629	983,778	985,585	983,689	987,294	994,279	996,305	1,000,312	1,026,262	1,039,871	1,052,702	1,000,994
FFS Members	91,378	99,920	100,302	93,871	98,749	99,972	99,615	99,252	99,928	109,012	94,359	89,482	97,987
OHP Basic with Medicare	8,912	9,279	9,365	9,067	9,362	9,174	8,622	8,495	7,620	7,613	7,275	7,121	8,492
OHP Basic without Medicare	11,793	11,967	12,047	11,869	12,431	12,040	11,882	11,860	11,739	11,470	11,412	11,281	11,816
ACA	70,673	78,674	78,890	72,935	76,956	78,758	79,111	78,897	80,569	89,929	75,672	71,080	77,679
Encounter Members	888,848	881,709	883,476	891,714	884,940	887,322	894,664	897,053	900,384	917,250	945,512	963,220	903,008
OHP Basic with Medicare	68,815	68,626	68,722	69,151	68,769	69,265	69,949	70,261	71,185	71,584	72,135	72,516	70,082
OHP Basic without Medicare	61,928	61,667	61,560	62,079	62,180	62,716	62,920	62,837	62,961	63,059	62,873	62,810	62,466
ACA	758,105	751,416	753,194	760,484	753,991	755,341	761,795	763,955	766,238	782,607	810,504	827,894	770,460

Gross Cost Figures for Drugs	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	YTD Sum
Total Amount Paid (FFS & Encounter)	$85,138,323	$83,167,131	$79,488,237	$88,422,372	$79,024,536	$85,013,873	$88,554,066	$83,331,122	$97,603,114	$85,388,516	$81,990,182	$88,797,194	$1,025,918,666
Mental Health Carve-Out Drugs	$8,769,601	$8,635,175	$8,051,390	$8,944,622	$8,121,560	$8,828,313	$9,311,298	$8,618,585	$9,526,710	$9,051,476	$8,783,162	$9,437,183	$106,079,076
OHP Basic with Medicare	$33,196	$41,678	$32,600	$39,134	$33,985	$42,387	$39,771	$32,745	$32,473	$30,950	$30,707	$36,154	$425,780
OHP Basic without Medicare	$3,469,032	$3,404,501	$3,092,328	$3,526,667	$3,185,567	$3,467,184	$3,663,960	$3,322,017	$3,685,587	$3,476,908	$3,282,562	$3,641,902	$41,218,215
ACA	$5,217,001	$5,138,556	$4,884,033	$5,331,585	$4,859,351	$5,264,253	$5,551,943	$5,206,547	$5,750,382	$5,495,679	$5,418,800	$5,713,004	$63,831,134
FFS Physical Health Drugs	$2,784,887	$2,713,427	$2,482,048	$2,920,418	$2,564,876	$2,689,760	$3,091,999	$2,777,460	$3,056,971	$2,919,828	$2,527,226	$2,566,756	$33,095,656
OHP Basic with Medicare	$54,037	$54,967	$55,092	$64,831	$56,764	$59,469	$64,072	$53,624	$60,466	$52,603	$44,212	$51,768	$671,906
OHP Basic without Medicare	$1,090,549	$977,813	$864,702	$1,097,580	$861,514	$915,467	$1,114,290	$1,003,794	$1,084,503	$1,003,622	$909,200	$912,500	$11,835,534
ACA	$1,522,871	$1,534,552	$1,429,936	$1,598,587	$1,514,424	$1,584,160	$1,757,720	$1,580,523	$1,772,674	$1,738,477	$1,451,154	$1,460,066	$18,945,143
FFS Physician Administered Drugs	$1,182,533	$1,281,530	$1,525,455	$1,513,090	$1,407,834	$1,287,998	$1,466,356	$1,629,686	$1,508,301	$1,145,918	$1,121,576	$1,426,441	$16,496,719
OHP Basic with Medicare	$129,213	$178,028	$164,039	$184,061	$144,249	$145,418	$151,058	$124,362	$92,060	$103,421	$115,093	$120,611	$1,651,614
OHP Basic without Medicare	$191,329	$158,834	$571,313	$413,746	$383,346	$224,354	$263,561	$531,493	$261,910	$141,949	$315,004	$459,570	$3,916,410
ACA	$360,357	$512,483	$412,295	$409,709	$498,465	$479,244	$607,869	$518,340	$429,374	$493,621	$328,547	$360,146	$5,410,449
Encounter Physical Health Drugs	$56,709,260	$55,852,095	$53,800,202	$59,496,764	$53,103,089	$56,841,145	$58,230,124	$55,182,217	$65,723,389	$57,799,325	$55,011,873	$58,899,703	$686,649,186
OHP Basic with Medicare	$770,168	$713,610	$731,812	$818,037	$757,101	$714,009	$852,276	$715,570	$843,937	$676,994	$676,720	$742,620	$9,012,851
OHP Basic without Medicare	$13,892,930	$13,434,226	$12,770,206	$14,341,497	$13,212,879	$14,164,619	$14,133,419	$13,299,699	$15,391,592	$14,094,263	$13,198,882	$14,078,130	$166,012,344
ACA	$41,394,987	$41,101,081	$39,673,171	$43,722,313	$38,596,086	$41,296,007	$42,564,527	$40,554,833	$48,703,852	$42,437,482	$40,504,100	$43,495,998	$504,044,436
Encounter Physician Administered Drugs	$15,692,042	$14,684,904	$13,629,143	$15,547,477	$13,827,176	$15,366,657	$16,454,289	$15,123,174	$17,787,743	$14,471,969	$14,546,344	$16,467,111	$183,598,029
OHP Basic with Medicare	$562,849	$494,448	$559,494	$609,657	$567,164	$558,008	$598,291	$582,852	$584,343	$489,929	$587,362	$607,906	$6,802,302
OHP Basic without Medicare	$2,988,365	$3,029,632	$2,745,573	$3,341,272	$2,704,028	$3,236,173	$3,664,256	$3,691,320	$3,464,346	$3,540,985	$3,388,838	$3,502,571	$39,297,360
ACA	$11,715,549	$10,838,606	$10,017,342	$11,271,961	$10,095,578	$11,046,281	$11,757,085	$10,580,319	$13,498,098	$10,237,782	$10,245,068	$11,969,876	$133,273,544

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

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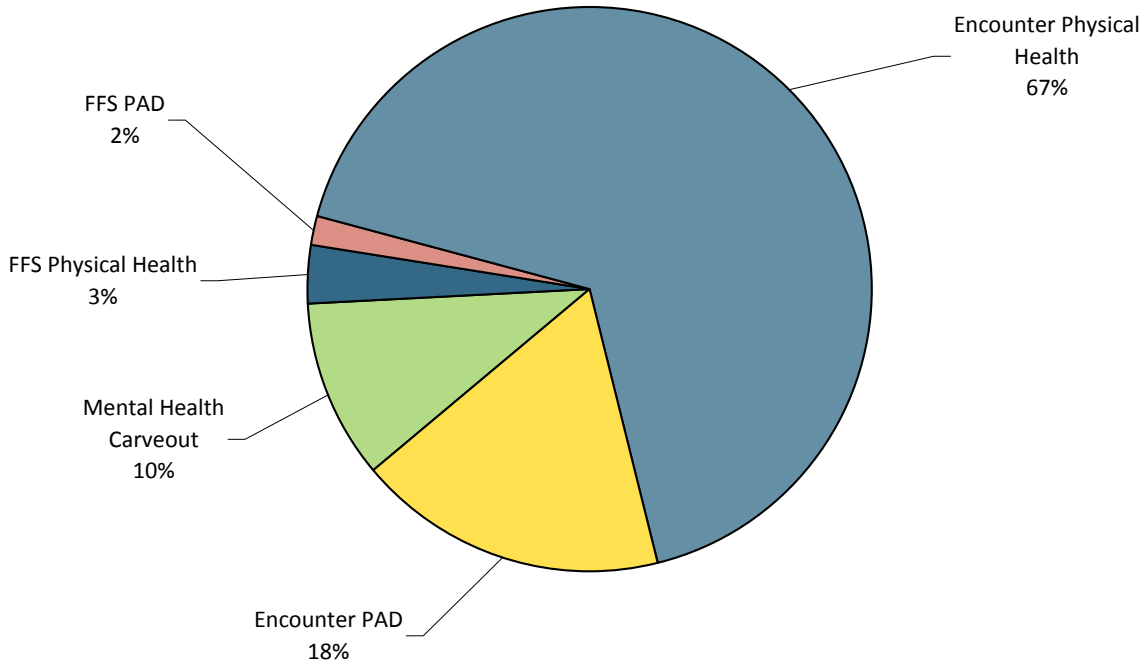
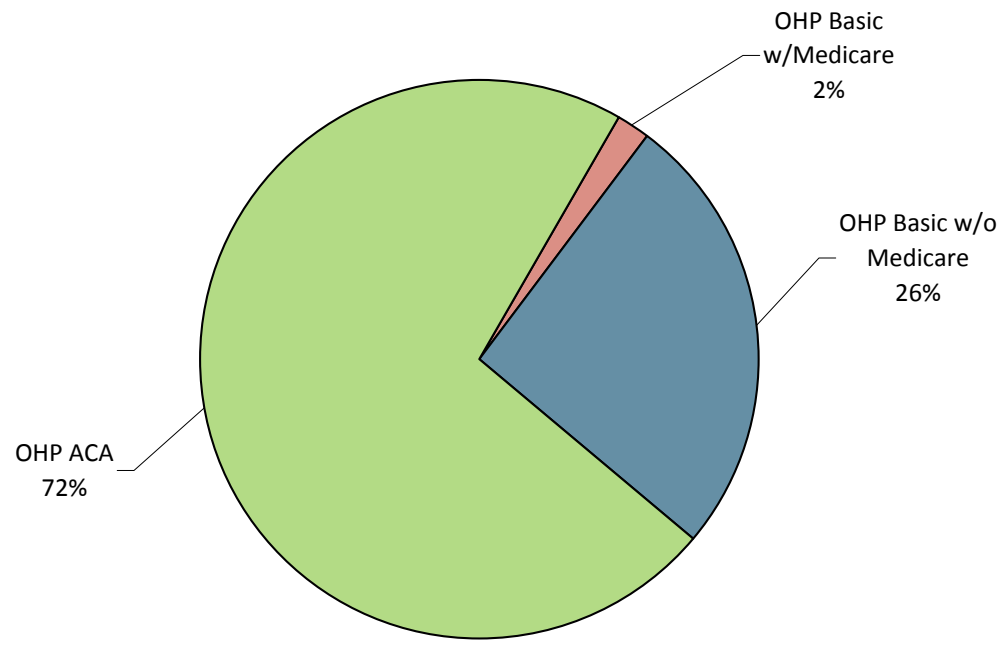
YTD Percent Paid Amounts





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

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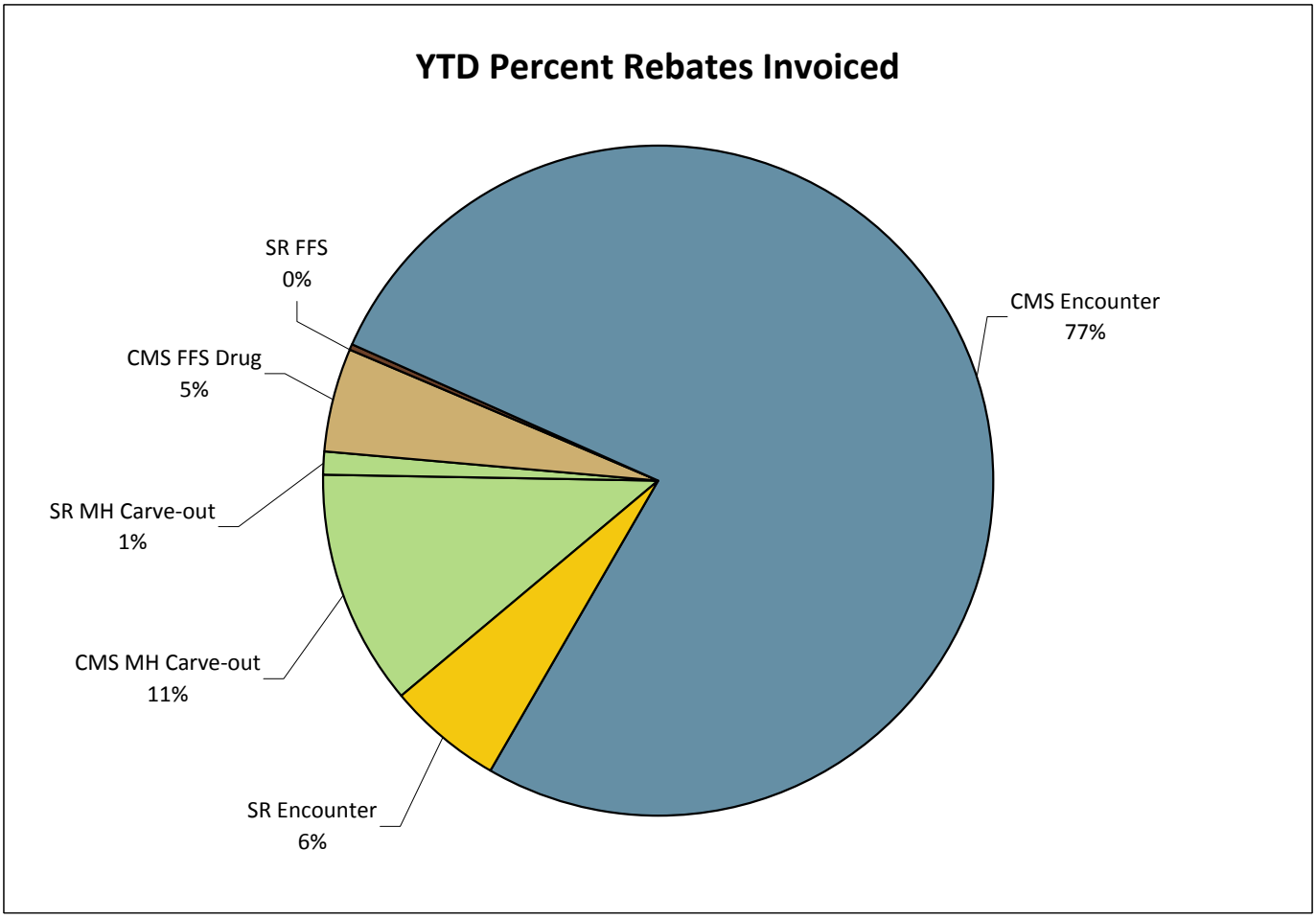
Quarterly Rebates Invoiced	2019-Q3	2019-Q4	2020-Q1	2020-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$105,079,627	$104,562,794	$114,025,181	$108,164,177	$431,831,779
CMS MH Carve-out	$11,213,281	$11,478,737	$13,590,728	$12,817,791	$49,100,536
SR MH Carve-out	$1,156,887	$1,269,765	$1,408,756	$1,330,995	$5,166,403
CMS FFS Drug	$5,079,675	$4,992,793	$5,898,826	$5,392,033	$21,363,327
SR FFS	$304,053	$329,635	$417,238	$473,576	$1,524,501
CMS Encounter	$82,556,928	$81,423,637	$85,827,473	$80,825,220	$330,633,257
SR Encounter	$4,768,803	$5,068,228	$6,882,161	$7,324,564	$24,043,755

Quaterly Net Drug Costs	2019-Q3	2019-Q4	2020-Q1	2020-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$142,714,065	$147,897,986	$155,463,121	$148,011,715	$594,086,887
Mental Health Carve-Out Drugs	$13,085,998	$13,145,993	$12,457,110	$13,123,036	$51,812,136
FFS Phys Health + PAD	$6,586,152	$7,061,550	$7,214,709	$5,842,137	$26,704,548
Encounter Phys Health + PAD	$123,041,915	$127,690,443	$135,791,302	$129,046,542	$515,570,203



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

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Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$86.86	$84.72	$80.80	$89.72	$80.33	$86.11	$89.06	$83.64	$97.57	$83.20	$78.85	$84.35	$85.43
Mental Health Carve-Out Drugs	$8.95	$8.80	$8.18	$9.08	$8.26	$8.94	$9.36	$8.65	$9.52	$8.82	$8.45	$8.96	$8.83
FFS Physical Health Drugs	$30.48	$27.16	$24.75	$31.11	$25.97	$26.91	$31.04	$27.98	$30.59	$26.78	$26.78	$28.68	$28.19
FFS Physician Administered Drugs	$12.94	$12.83	$15.21	$16.12	$14.26	$12.88	$14.72	$16.42	$15.09	$10.51	$11.89	$15.94	$14.07
Encounter Physical Health Drugs	$63.80	$63.35	$60.90	$66.72	$60.01	$64.06	$65.09	$61.52	$72.99	$63.01	$58.18	$61.15	$63.40
Encounter Physician Administered Drugs	$17.65	$16.66	$15.43	$17.44	$15.62	$17.32	$18.39	$16.86	$19.76	$15.78	$15.38	$17.10	$16.95

Claim Counts	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Total Claim Count (FFS & Encounter)	1,071,285	1,050,390	1,028,840	1,105,625	1,007,730	1,079,832	1,113,472	1,042,630	1,144,408	982,569	990,413	1,048,218	1,055,451
Mental Health Carve-Out Drugs	165,130	161,538	156,870	167,827	154,082	164,554	169,851	157,743	177,068	164,881	164,299	172,305	164,679
FFS Physical Health Drugs	43,095	42,354	41,644	43,814	39,789	42,314	46,536	42,278	45,983	41,248	37,710	39,190	42,163
FFS Physician Administered Drugs	12,459	12,068	11,521	12,046	10,477	11,697	12,910	11,381	9,990	8,693	9,568	9,815	11,052
Encounter Physical Health Drugs	725,942	708,038	698,113	755,337	683,403	734,577	759,790	714,942	807,653	686,255	678,384	716,122	722,380
Encounter Physician Administered Drugs	124,659	126,392	120,692	126,601	119,979	126,690	124,385	116,286	103,714	81,492	100,452	110,786	115,177

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$79.47	$79.18	$77.26	$79.98	$78.42	$78.73	$79.53	$79.92	$85.29	$86.90	$82.78	$84.71	$81.01
Mental Health Carve-Out Drugs	$53.11	$53.46	$51.33	$53.30	$52.71	$53.65	$54.82	$54.64	$53.80	$54.90	$53.46	$54.77	$53.66
FFS Physical Health Drugs	$64.62	$64.07	$59.60	$66.65	$64.46	$63.57	$66.44	$65.70	$66.48	$70.79	$67.02	$65.50	$65.41
FFS Physician Administered Drugs	$94.91	$106.19	$132.41	$125.61	$134.37	$110.11	$113.58	$143.19	$150.98	$131.82	$117.22	$145.33	$125.48
Encounter Physical Health Drugs	$78.12	$78.88	$77.07	$78.77	$77.70	$77.38	$76.64	$77.18	$81.38	$84.22	$81.09	$82.25	$79.22
Encounter Physician Administered Drugs	$125.88	$116.19	$112.92	$122.81	$115.25	$121.29	$132.29	$130.05	$171.51	$177.59	$144.81	$148.64	$134.93

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.18	$19.35	$19.24	$19.46	$18.83	$19.04	$19.46	$19.72	$20.06	$19.52	$19.13	$19.43	$19.37
Mental Health Carve-Out Drugs	$18.40	$18.21	$17.41	$17.52	$17.57	$17.69	$17.54	$17.51	$16.67	$16.78	$16.87	$16.95	$17.43
FFS Physical Health Drugs	$19.09	$19.76	$19.17	$21.32	$20.59	$20.08	$21.12	$19.79	$20.11	$20.93	$20.13	$19.87	$20.16
Encounter Physical Health Drugs	$19.39	$19.61	$19.71	$19.85	$19.05	$19.32	$19.84	$20.25	$20.88	$20.16	$19.68	$20.07	$19.82

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$494.87	$503.60	$466.91	$468.97	$488.03	$497.99	$499.74	$508.46	$523.90	$559.74	$534.31	$555.39	$508.49
Mental Health Carve-Out Drugs	$1,078.09	$1,073.32	$1,048.08	$1,074.30	$1,059.38	$1,063.80	$1,103.24	$1,094.89	$1,104.65	$1,114.55	$1,103.44	$1,115.05	$1,086.07
FFS Physical Health Drugs	$264.27	$262.64	$233.16	$257.49	$257.51	$249.93	$266.64	$277.17	$270.60	$287.98	$271.52	$266.55	$263.79
Encounter Physical Health Drugs	$480.70	$490.00	$454.31	$452.82	$473.62	$484.74	$483.44	$491.73	$510.34	$546.76	$518.73	$541.03	$494.02

Generic Drug Use Percentage	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Generic Drug Use Percentage	88.7%	88.8%	88.3%	87.9%	88.5%	88.8%	89.0%	89.1%	88.9%	89.1%	89.1%	89.4%	88.8%
Mental Health Carve-Out Drugs	96.7%	96.7%	96.7%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.5%	96.6%	96.6%	96.6%
FFS Physical Health Drugs	81.4%	81.8%	81.1%	80.8%	81.5%	81.1%	81.5%	82.2%	81.5%	81.3%	81.3%	81.5%	81.4%
Encounter Physical Health Drugs	87.3%	87.4%	86.8%	86.4%	87.1%	87.5%	87.7%	87.9%	87.6%	87.8%	87.7%	88.1%	87.4%

Preferred Drug Use Percentage	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Avg Monthly
Preferred Drug Use Percentage	85.40%	85.32%	85.24%	85.03%	85.42%	85.48%	85.19%	85.10%	85.18%	84.92%	84.82%	85.06%	85.2%
Mental Health Carve-Out Drugs	73.18%	73.18%	73.23%	73.31%	73.11%	73.03%	73.13%	73.06%	73.28%	73.15%	72.87%	73.05%	73.1%
FFS Physical Health Drugs	94.50%	94.58%	94.58%	94.56%	94.68%	94.96%	94.68%	94.29%	93.75%	89.25%	89.21%	89.00%	93.2%
Encounter Physical Health Drugs	87.62%	87.53%	87.40%	87.12%	87.68%	87.75%	87.32%	87.24%	87.29%	87.44%	87.41%	87.68%	87.5%

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 21, 2021

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 2020

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,555,874	16.8%	5,471	$1,198	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,234,007	8.3%	1,607	$2,012	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,296,924	5.9%	2,085	$1,102	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,740,244	4.5%	872	$1,996	Y
5	REXULTI	Antipsychotics, 2nd Gen	$1,659,886	4.2%	1,548	$1,072	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$812,014	2.1%	132	$6,152	Y
7	ARISTADA	Antipsychotics, Parenteral	$664,851	1.7%	293	$2,269	Y
8	TRINTELLIX	Antidepressants	$645,179	1.7%	1,629	$396	V
9	BUPROPION XL	Antidepressants	$624,145	1.6%	32,617	$19	V
10	SERTRALINE HCL	Antidepressants	$546,346	1.4%	53,094	$10	Y
11	VIIBRYD	Antidepressants	$527,817	1.4%	1,777	$297	V
12	SAPHRIS	Antipsychotics, 2nd Gen	$502,930	1.3%	713	$705	Y
13	DULOXETINE HCL	Antidepressants	$483,104	1.2%	33,914	$14	V
14	FLUOXETINE HCL	Antidepressants	$460,721	1.2%	38,395	$12	Y
15	TRAZODONE HCL	Antidepressants	$454,114	1.2%	44,561	$10	
16	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$398,040	1.0%	2	$199,020	
17	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$358,506	0.9%	1,929	$186	V
18	BIKTARVY	HIV	$344,743	0.9%	128	$2,693	Y
19	ESCITALOPRAM OXALATE	Antidepressants	$343,808	0.9%	33,552	$10	Y
20	ATOMOXETINE HCL*	ADHD Drugs	$324,998	0.8%	5,826	$56	Y
21	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$309,030	0.8%	350	$883	Y
22	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$307,713	0.8%	22,646	$14	
23	LAMOTRIGINE	Antiepileptics (non-injectable)	$285,469	0.7%	26,396	$11	Y
24	VENLAFAXINE HCL ER	Antidepressants	$259,595	0.7%	2,007	$129	V
25	CHOLBAM*	Bile Therapy	$248,996	0.6%	6	$41,499	N
26	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$222,587	0.6%	2,449	$91	V
27	VENLAFAXINE HCL ER	Antidepressants	$221,108	0.6%	17,045	$13	Y
28	TRIKAFTA*	Cystic Fibrosis	$215,278	0.6%	18	$11,960	N
29	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$212,089	0.5%	17,206	$12	Y
30	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$210,631	0.5%	18,554	$11	Y
31	AMITRIPTYLINE HCL*	Antidepressants	$209,154	0.5%	14,764	$14	Y
32	Gammagard Liquid Injection	Physican Administered Drug	$204,719	0.5%	29	$7,059	
33	Inj Pembrolizumab	Physican Administered Drug	$203,493	0.5%	48	$4,239	
34	LANTUS SOLOSTAR*	Diabetes, Insulins	$196,585	0.5%	524	$375	Y
35	CITALOPRAM HBR	Antidepressants	$189,479	0.5%	21,481	$9	Y
36	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$178,750	0.5%	44	$4,063	Y
37	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$160,946	0.4%	14	$11,496	Y
38	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$159,259	0.4%	595	$268	V
39	CONCERTA*	ADHD Drugs	$156,086	0.4%	553	$282	N
40	OLANZAPINE	Antipsychotics, 2nd Gen	$149,894	0.4%	11,613	$13	Y
		Top 40 Aggregate:	**$27,279,109**		**416,487**	**$7,542**	
		All FFS Drugs Totals:	**$39,083,321**		**669,160**	**$542**	

*** 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

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2020

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$398,040	3.9%	2	$199,020	
2	BIKTARVY	HIV	$344,743	3.4%	128	$2,693	Y
3	CHOLBAM*	Bile Therapy	$248,996	2.4%	6	$41,499	N
4	TRIKAFTA*	Cystic Fibrosis	$215,278	2.1%	18	$11,960	N
5	Gammagard Liquid Injection	Physican Administered Drug	$204,719	2.0%	29	$7,059	
6	Inj Pembrolizumab	Physican Administered Drug	$203,493	2.0%	48	$4,239	
7	LANTUS SOLOSTAR*	Diabetes, Insulins	$196,585	1.9%	524	$375	Y
8	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$178,750	1.7%	44	$4,063	Y
9	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$160,946	1.6%	14	$11,496	Y
10	CONCERTA*	ADHD Drugs	$156,086	1.5%	553	$282	N
11	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$124,737	1.2%	5	$24,947	
12	Etonogestrel Implant System	Physican Administered Drug	$110,106	1.1%	166	$663	
13	ELIQUIS	Anticoagulants, Oral and SQ	$107,729	1.1%	295	$365	Y
14	VYVANSE*	ADHD Drugs	$106,845	1.0%	665	$161	Y
15	Inj, Atezolizumab,10 Mg	Physican Administered Drug	$99,036	1.0%	17	$5,826	
16	Aflibercept Injection	Physican Administered Drug	$96,743	0.9%	164	$590	
17	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$93,792	0.9%	11	$8,527	
18	STELARA*	Biologics for Autoimmune Conditions	$90,130	0.9%	11	$8,194	N
19	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$87,926	0.9%	1,444	$61	Y
20	IBRANCE*	Antineoplastics, Newer	$87,418	0.9%	8	$10,927	
21	Mirena, 52 Mg	Physican Administered Drug	$84,787	0.8%	140	$606	
22	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$83,596	0.8%	2,268	$37	Y
23	VIMPAT	Antiepileptics (non-injectable)	$82,150	0.8%	182	$451	Y
24	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$82,113	0.8%	150	$547	Y
25	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$81,658	0.8%	21	$3,888	Y
26	PULMOZYME	Cystic Fibrosis	$79,258	0.8%	37	$2,142	Y
27	LEVEMIR FLEXTOUCH	Diabetes, Insulins	$75,198	0.7%	142	$530	Y
28	VIGABATRIN	Antiepileptics (non-injectable)	$69,683	0.7%	7	$9,955	N
29	FLOVENT HFA	Corticosteroids, Inhaled	$69,380	0.7%	429	$162	Y
30	TRIUMEQ	HIV	$67,715	0.7%	26	$2,604	Y
31	LANTUS	Diabetes, Insulins	$66,567	0.6%	176	$378	Y
32	NOVOLOG FLEXPEN	Diabetes, Insulins	$65,939	0.6%	124	$532	Y
33	Inj Trastuzumab Excl Biosimi	Physican Administered Drug	$65,388	0.6%	16	$4,087	
34	XULANE	STC 63 - Oral Contraceptives	$64,844	0.6%	379	$171	
35	HUMIRA*	Biologics for Autoimmune Conditions	$63,615	0.6%	7	$9,088	Y
36	CREON	Pancreatic Enzymes	$62,070	0.6%	51	$1,217	Y
37	AFINITOR DISPERZ*	Antineoplastics, Newer	$61,247	0.6%	10	$6,125	
38	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$60,879	0.6%	433	$141	
39	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$60,584	0.6%	6	$10,097	N
40	ADVATE	Antihemophilia Factors	$59,371	0.6%	3	$19,790	
		Top 40 Aggregate:	**$4,718,140**		**8,759**	**$10,387**	
		All FFS Drugs Totals:	**$10,250,425**		**128,441**	**$558**	

*** Drug requires Prior Authorization**

Notes
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Last updated: January 21, 2021

ProDUR Report for October through December 2020

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	6	6	0	0	0.01%	100.0%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,775	393	0	1,380	1.43%	22.1%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	244	50	0	194	0.17%	20.5%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	81,498	14,113	238	67,147	68.27%	17.3%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	25,461	6,194	7	19,248	21.30%	24.3%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	770	121	0	649	0.60%	15.7%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	2	1	0	1	0.00%	50.0%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	817	209	0	608	0.63%	25.6%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	458	132	0	326	0.33%	28.8%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	20	16	0	4	0.03%	80.0%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	8,245	2,114	0	6,128	6.87%	25.6%
		Totals	**119,296**	**23,349**	**245**	**95,685**	**99.65%**	**19.6%**

ProDUR Report for October through December 2020

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)	1,551	239	1,314	13,036	11.9%	15.4%
ER	Lorazepam	364	94	270	12,523	2.9%	25.8%
ER	Alprazolam	215	39	176	8,012	2.7%	18.1%
ER	Diazepam	124	34	90	4,279	2.9%	27.4%
ER	Buspirone (Buspar)	2,858	429	2,429	29,159	9.8%	15.0%
ER	Lamictal (Lamotrigine)	5,064	871	4,192	39,857	12.7%	17.2%
ER	Seroquel (Quetiapine)	4,027	842	3,184	29,421	13.7%	20.9%
ER	Zyprexa (Olanzapine)	2,393	482	1,911	18,361	13.0%	20.1%
ER	Risperdal (Risperidone)	1,832	374	1,458	13,014	14.1%	20.4%
ER	Abilify (Aripiprazole)	3,144	482	2,662	24,556	12.8%	15.3%
ER	Wellbutrin (Bupropion)	5,420	869	4,551	61,263	8.8%	16.0%
ER	Hydrocodone/APAP	7	2	5	824	0.8%	28.6%
ER	Oxycodone	8	7	1	1,179	0.7%	87.5%
ER	Suboxone (Buprenorphine/Naloxone)	85	33	52	1,884	4.5%	38.8%
ER	Zoloft (Sertraline)	6,734	1,180	5,554	68,879	9.8%	17.5%
ER	Prozac (Fluoxetine)	4,555	724	3,831	48,170	9.5%	15.9%
ER	Lexapro (Escitalopram)	4,116	604	3,511	42,863	9.6%	14.7%
ER	Celexa (Citalopram)	2,093	260	1,833	25,516	8.2%	12.4%
ER	Trazodone	6,040	976	5,063	57,145	10.6%	16.2%
ER	Cymbalta (Duloxetine)	4,184	634	3,550	41,800	10.0%	15.2%
ER	Intuniv (Guanfacine)	1,668	183	1,485	11,896	14.0%	11.0%

ProDUR Report for October through December 2020

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	3,303	73	200	760	4	1,940	218	0	108
ER	November	3,645	98	240	839	3	2,082	249	0	134
ER	December	3,204	98	191	781	2	1,873	163	2	94
	Total =	**10,152**	**269**	**631**	**2,380**	**9**	**5,895**	**630**	**2**	**336**
	Percentage of total overrides =		**2.6%**	**6.2%**	**23.4%**	**0.1%**	**58.1%**	**6.2%**	**0.0%**	**3.3%**

ProDUR Cost Savings Chart 4Q2020

Cost Savings Methodology

The pharmacist will receive a denial for an early refill alerted claims. After receiving a denied ProDUR alert, the pharmacist may choose to override the alert, cancel the claim, resubmit a different claim, or take no action. The cost savings due to claims that were not dispensed because of these alerts is defined as being cancelled and then not being reprocessed again at a later date.

Early Refill Cost Saving		
	ER Claims Cancelled	ER Cost Savings
October-20	186	$43,940.80
November-20	14	$3,496.95
December-20	38	$10,355.63
Total	**238**	**$57,793.38**

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 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	23			
		Unique Patients Identified	23			
		Total Faxes Successfully Sent	15			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	7			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$226			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	146	27		
		Unique Patients Identified	147	28		
		Total Faxes Successfully Sent	99	18		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	59	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$21,953	$71		

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

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	51	2		
		Total Faxes Successfully Sent	10	1		
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	3			
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	7			
		Safety Monitoring Profiles Identified	5			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$691			

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified	936			
		Profiles sent for expert review	13			
		Prescribers successfully notified	10			
		Patients with change in antipsychotic drug in following 90 days	2			
		Patients with continued antipsychotic therapy in the following 90 days	6			

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

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	69	11		
		Total prescribers identified	68	11		
		Prescribers successfully notified	68			
		Patients with claims for the same antipsychotic within the next 90 days	33			
		Patients with claims for a different antipsychotic within the next 90 days	5			

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	75	19		
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	18	2		
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	113	43		
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	17	4		
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed	10			
		RetroDUR_Letters Sent To Providers	4			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
	Lock-In	RetroDUR_Profiles Reviewed	13			
		RetroDUR_Letters Sent To Providers	2			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
		Locked In	1			
	Polypharmacy	RetroDUR_Profiles Reviewed	29	2		
		RetroDUR_Letters Sent To Providers	6			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			

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

Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Combination Opioid-Sedative	Total patients identified	120	4		
		Total prescribers identified	119	4		
		Prescribers successfully notified	112			
		Patients with discontinuation of therapy within next 90 days	53	4		
		Patients with new prescription for naloxone within next 90 days	3			
		Average number of sedative drugs dispensed within next 90 days	0	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	0	0		
	ICS/LABA	Disqualified	6	2		
		Disqualified - Erroneous denial	6	2		
		Faxes Sent	1			
		Fax Sent - Combination Inhaler	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			
	TCAs in Children	Total patients identified	10	1		
		Total prescribers identified	10	1		
		Prescribers successfully notified	7			

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New Disease-Modifying Anti-Rheumatic Drugs for Management of Rheumatoid Arthritis

Deanna Moretz, Pharm.D., BCPS, Oregon State University Drug Use Research and Management Group

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity.[1] Inflammation in RA is mediated by activation of T-cells, B-cells and macrophages which leads to expression of cytokines such as tumor necrosis factor (TNF) and interleukins (IL).[1] Biologic or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs or tsDMARDs) are recommended for patients with a suboptimal response or intolerance to Conventional Synthetic Disease-Modifying Anti-Rheumatic drugs (csDMARDs), such as methotrexate (MTX), sulfasalazine, hydroxychloroquine or leflunomide **(Table1)**.[2,3] Biosimilar agents are available for adalimumab, infliximab and etanercept. The purpose of this newsletter is to review the efficacy and safety for 3 recently approved DMARDs to manage RA: sarilumab, baricitinib, and upadacitinib.

Table 1. FDA-approved bDMARDs and tsDMARDs to Manage RA[4,5]

Drug - Route of Administration	Molecular Target
Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs)	
Adalimumab – SC (HUMIRA)	TNF
Certolizumab Pegol – SC (CIMZIA)	
Etanercept – SC (ENBREL)	
Golimumab - IV or SC (SIMPONI and SIMPONIARIA)	
Infliximab – IV (REMICADE)	
Sarilumab – SC (KEVZARA)	IL-6 Receptor
Tocilizumab – IV or SC (ACTEMRA)	
Anakinra – SC (KINERET)	IL-1
Rituximab – IV (RITUXAN)	B-lymphocyte
Abatacept - IV or SC (ORENCIA)	T-lymphocyte
Targeted Synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)	
Tofacitinib – PO (XELJANZ)	JAK 1,2,3
Baricitinib – PO (OLUMIANT)	JAK 1,2
Upadacitinib – PO (RINVOQ)	JAK 1
Abbreviations: FDA=Food and Drug Administration; IL=interleukin; IV = intravenous; JAK=Janus kinase; PO=oral; RA =rheumatoid arthritis; SC = subcutaneous; TIM=targeted immune therapy; TNF = tumor necrosis factor	

Assessment of Efficacy for Rheumatoid Arthritis Therapies

Primary endpoints frequently studied in clinical trials for RA therapies include the American College of Rheumatology (ACR) response and the 28-joint Disease Activity Score (DAS-28). The ACR20 is a composite measure defined as a 20% improvement in the number of tender and swollen joints, and a 20% improvement in 3 of the following 5 criteria: patient global assessment, physician global assessment, visual analog pain scale, patient assessment of physical functioning, and either erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP).[6] ACR50 and ACR70 criteria are similar, but with improvement of at least 50% and 70% in ACR criteria, respectively.[6] The DAS-28 is another index of disease activity. The DAS-28 is a composite outcome that consists of: 1) the number of painful joints; 2) number of swollen joints; 3) ESR or CRP and 4) patient assessment of disease activity.[7] A DAS-28 score greater than 5.1 corresponds to high disease activity and a score of less than 3.2 corresponds to low disease activity.[7]

Sarilumab: IL-6 Receptor Inhibitor

Sarilumab and tocilizumab bind to IL-6 receptors which inhibits IL-6 mediated signaling. Tocilizumab binds to the entire IL-6 receptor, while sarilumab targets the alpha subunit of the receptor.[8] Sarilumab is approved for the treatment of adult patients with moderate-to-severe RA who have had an inadequate response to one or more DMARDs.[9] Sarilumab may be used as monotherapy or in combination with other csDMARDs. The recommended dose is 200 mg subcutaneously every 2 weeks. The dose should be reduced to 150 mg in patients with neutropenia, thrombocytopenia, or elevated liver enzymes.[9] The Food and Drug Administration (FDA) approval was based on 3 randomized clinical trials (RCTs) in which efficacy and safety of sarilumab was compared to placebo or adalimumab.[10-12] Details of each study are provided in **Table 2**.

Table 2. Clinical Trial Data for Sarilumab

Trial Name	Comparators	ACR 20 Response at Week 24	ARR/NNT
MOBILITY B[10] n=1,197	SARI 150 mg vs. PBO SARI 300 mg vs. PBO	ACR20: 58% vs. 22% ACR20: 66% vs. 22%	36%/3 44%/3 P<0.0001 for both 95% CI NR
TARGET[11] n=546	SARI 150 mg vs. PBO SARI 300 mg vs. PBO	ACR20: 56% vs. 34% ACR20: 61% vs. 34%	22%/5 27%/4 P<0.0001 for both 95% CI NR
MONARCH[12] n=346	SARI 200 mg vs. ADA 40 mg every 2 weeks	72% 59%	13%/8 P<0.0074 95% CI NR
Abbreviations: ACR= American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; CI=confidence interval; NNT=number needed to treat; NR=not reported; PBO=placebo; SARI=sarilumab			

Similar to other DMARDs, sarilumab includes an FDA black boxed warning for risk of serious infections.[9] Labeling for sarilumab also has warnings for neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, gastrointestinal perforation, hypersensitivity, and co-administration with live vaccines.[9] These warnings are similar to those for tocilizumab.

Baricitinib and Upadacitinib: JAK inhibitors

JAK inhibitors are among the newest class of treatments for RA. JAK proteins are implicated in the pathogenesis of RA as they play an important role in the signalling pathways of various cytokines, growth factors, and hormones involved in immunity and hematopoiesis.[13] Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved and each has a different inhibitory profile for the JAK proteins (see **Table 1**). JAK inhibitors are potent immunosuppressants. There are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy, lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia, and lipid elevations.[14] Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue for JAK inhibitors.[15]

Baricitinib is an oral JAK inhibitor approved for treatment of adult patients with moderate-to-severe RA who have had an inadequate response to one or more TNF inhibitor (TNFi) therapies.[16] The recommended daily dose is 2 mg once a day as monotherapy or in combination with MTX.[16] The efficacy and safety of baricitinib was assessed in 4 phase 3 RCTs.[17-20] Baricitinib 2 and 4 mg doses were compared to placebo in adults with RA who had an inadequate response to MTX (RA-BEAM), an inadequate response to csDMARDs (RA-BUILD), and in patients refractory to TNFis (RA-BEACON).[13] In all trials except for RA-BEGIN, patients continued background MTX therapy. Results of the primary endpoint in these trials, ACR20 response at week 12 or 24, are summarized in **Table 3.** In the 3 placebo-controlled trials, baricitinib was superior to placebo in achieving ACR20 response. In RA-BEAM, baricitinib was compared to adalimumab as noninferiority endpoint (estimated power for test of noninferiority, 93%; prespecified noninferiority margin of 12%).[18] Baricitinib was found to be noninferior to adalimumab at week 12 for the ACR20 response.[18] According to the pre-specified statistical analysis plan, baricitinib was also considered to be superior to adalimumab based on ACR20 response at 12 weeks (P≤0.05).[18]

Table 3. Clinical Trial Data for Baricitinib

Trial Name	Comparators	ACR 20 Response at Week 12	ARR/NNT
RA-BEGIN[17] n=588	BARI 4 mg daily vs. oral MTX weekly	77% vs. 62%* *Week 24	15%/7 95% CI NR; P≤0.05
RA-BEAM[18] n=1,307	BARI 4 mg daily vs. PBO BARI 4 mg daily vs. ADA 40 mg every other week	70% vs. 40% 70% vs. 61%	30%/4 95% CI NR; p≤0.001 9%/12 95% CI NR; P≤0.05
RA-BUILD[19] n=684	BARI 2 mg daily vs. PBO BARI 4 mg daily vs. PBO	66% vs. 39% 62% vs. 39%	27%/4 95% CI NR; P≤0.001 23%/5 95% CI NR; P≤0.001
RA-BEACON[20] n=527	BARI 2 mg daily vs. PBO BARI 4 mg daily vs. PBO	49% vs. 27% 55% vs. 27%	22%/5 95% CI NR; P<0.001 28%/4 95% CI NR; P<0.001

Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; BARI=baricitinib; CI=confidence interval; MTX=methotrexate; NNT=number needed to treat; NR=not reported; PBO=Placebo

The most common adverse effects noted in clinical trials with baricitinib 2 mg and 4 mg were upper respiratory tract infections (14-16%), nausea (3%), and herpes infections (0.8-1.8%).[16] There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with baricitinib compared to other treatments for moderate-to-severe RA.

Upadacitinib is an oral selective JAK-1 inhibitor indicated for the treatment of adults with moderate-to-severe RA who have had an inadequate response or intolerance to MTX.[21]. Approval of upadacitinib was based on 4 phase 3 RCTs conducted in adults with moderate-to-severe RA.[22-25] The SELECT-NEXT and SELECT-COMPARE trials included adults with an inadequate response to csDMARDs. The SELECT-BEYOND trial included patients with an inadequate response to bDMARDs. Background csDMARDs were continued in all of the placebo-controlled trials. Two doses of upadacitinib (15 mg and 30 mg once daily) were studied in the trials; however due to safety concerns with the 30 mg dose (e.g. anemia, neutropenia), only the 15 mg dose was approved. The SELECT-COMPARE trial was also designed to test for the noninferiority and superiority of upadacitinib to adalimumab. Results for the trials are summarized in **Table 4.**

Table 4. Clinical Trial Data for Upadacitinib

Trial Name	Comparators	ACR 20 at week 12	ARR/NNT
SELECT-MONOTHERAPY[22] n=648	UPA 15 mg daily vs. oral MTX weekly UPA 30 mg daily vs. oral MTX weekly	68% vs. 41% 71% vs. 41%	27%/4 95% CI 18 to 36 p≤0.0001 30%/4 95% CI 21 to 39 p≤0.0001
SELECT-NEXT[23] n=661	UPA 15 mg daily vs. PBO UPA 30 mg daily vs. PBO	64% vs. 36% 66% vs. 36%	28%/4 95% CI 19 to 37 p<0.0001 30%/4 95% CI 22 to 39 p<0.0001
SELECT-COMPARE[24] n=1,629	UPA 15 mg daily vs. PBO UPA 15 mg daily vs. ADA 40 mg every other week	71% vs. 36% 63% vs. 36%	34%/3 95% CI 29 to 39 p≤0.001 8%/13 95% CI, 1 to 14 p≤0.05
SELECT-BEYOND[25] n=499	UPA 15 mg daily vs. PBO UPA 30 mg daily vs. PBO	65% vs. 28% 56% vs. 28%	37%/3 95% CI 26 to 46 p<0.0001 28%/4 95% CI 18 to 38 P<0.0001

Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; CI=confidence interval; MTX= methotrexate; NNT=number needed to treat; NR=not reported; PBO=Placebo; UPA=upadacitinib

Reported safety data from these trials demonstrated that patients treated with upadacitinib 15 mg experienced greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough, and pyrexia.[21] Upadacitinib and baricitinib prescribing information contains FDA black boxed warnings for serious infections leading to hospitalization or death, risk of lymphoma, and fatal thrombosis associated with JAK inhibitor administration.[16,21] Upadacitinib and baricitinib are not recommended for use in combination with other JAK inhibitors, bDMARDs, or with immunosuppressants such as azathioprine or cyclosporine.[16, 21]

In the Medicaid Fee-For-Service population, adalimumab and etanercept are preferred agents. All of the biologic agents require prior authorization to ensure safe and appropriate use.

Conclusions

Three DMARDs recently received FDA-approval to manage moderate-to-severe RA in adults who have had an inadequate response to MTX or other DMARDs. Sarilumab joins tocilizumab as a second SC IL-6 inhibitor treatment option. Two additional JAK inhibitors, baricitinib and upadacitinib, provide more oral options for patients unable to tolerate MTX or TNFis.

Peer Reviewed By: Cong-Qui Chu, M.D., Ph.D., Associate Professor of Medicine, Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University, Portland, Oregon and Andrew Gibler, Pharm.D., Director of Pharmacy, Legacy Mount Hood Medical Center, Gresham, Oregon.

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Cardiovascular Outcomes Associated with Newer Therapy Classes for Type 2 Diabetes Mellitus

Kathy Sentena, Pharm.D. Drug Use Research and Management, Oregon State University College of Pharmacy

There is a well-established correlation between type 2 diabetes mellitus (T2DM) and an increased risk of adverse cardiovascular (CV) outcomes. Cardiovascular disease affects approximately 32.2% of patients with T2DM on a global scale, responsible for around 50% of the mortality in patients with T2DM.[1] In 2008, the Food and Drug Administration (FDA) started to require drug manufacturers to conduct cardiovascular outcome trials to verify that the newer diabetes therapies for T2DM were void of increased risk (≤ 30%) of adverse CV effects.[2] The majority of newer diabetes therapies have completed CV outcome trials, assessing CV safety by analyzing major adverse CV events (MACE): CV death, nonfatal myocardial infarction (MI), and stroke. The focus of this newsletter will summarize the findings of the Drug Effectiveness Review Project (DERP) report on CV outcomes with the newer therapy classes for T2DM as well as review the evidence behind the new heart failure (HF) indication for dapagliflozin.

Drug Effectiveness Review Project Report on Newer Diabetes Therapies and CV Outcomes

The DERP looked specifically at the CV outcomes with the newer diabetes therapies (**Table 1**).[2] Eligible studies included randomized clinical trials and prospective or retrospective cohort studies (≥10,000 patients) published from January 1, 2017 to October 2, 2019.[2] Sixteen randomized controlled trials (RCTs) were identified including 15 placebo-controlled trials and one active control trial.[2] Ten of the RCTs were new to this review and six RCTs were from the original systematic review done by DERP in 2017.[2] Trials included adult patients with T2DM which were managed with standard of care therapy for glucose control and CV risk management. Important efficacy outcomes were mortality (all-cause and CV), and CV events (fatal or non-fatal MI, fatal or nonfatal stroke, and hospitalization for heart failure).

Table 1. Drugs Included in the DERP Report on Newer Diabetes Therapies and Cardiovascular Outcomes†[2]

Class	Generic Names	Brand Names
SGLT-2 inhibitors	Ertugliflozin Empagliflozin Dapagliflozin Canagliflozin	Steglatro* Jardiance Farxiga Invokana
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
GLP-1 receptor agonists	Oral semaglutide Subcutaneous semaglutide Lixisenatide Dulaglutide Albiglutide Exenatide ER Liraglutide Exenatide	Rybelsus Ozempic Adlyxin Trulicity Tanzeum‡ Bydureon Victoza Byetta

Abbreviations: DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2
Key: † Combination products were included for all classes; * No studies met inclusion criteria; ‡ No longer on the market

The CV outcome evidence compiled by DERP for the newer diabetes therapy classes are presented in **Table 2**. The glucagon-like peptide 1 receptor agonists (GLP-1 RAs) were the only drug class that demonstrated a small risk reduction in all-cause mortality, with approximately a 1% absolute difference between active therapy and placebo (number needed to treat [NNT] of 71-100 over 2.1 to 3.8 years).[2] As a class, the dipeptidyl peptidase-4 (DPP-4) inhibitors had a neutral effect on CV outcomes; however, there was a higher risk of heart failure (HF) for saxagliptin compared to placebo (3.5% vs. 2.8%; number needed to harm [NNH] 143 with a median follow up of 2.1 years).[2] There was moderate quality of evidence that sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduced the risk for hospitalizations due to heart failure with a NNT of 42 to 80 (mean follow up of 2.6 to 4.2 years).[2]

Table 2. Cardiovascular Outcomes for Classes of Newer Diabetes Therapies versus Placebo[2]

Outcome	All-Cause Mortality	Stroke	Myocardial Infarction	Hospitalization for HF
GLP-1 RAs *Pooled results from 7 trials*	***Small risk reduction*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No conclusion**** *(very low QoE)†*	***No effect*** *(moderate QoE)†*
DPP- 4 Inhibitors *Pooled results from 5 trials*	***No effect*** *(moderate QoE)†*	***No effect*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No effect*** *(low QoE)†*
SGLT-2 Inhibitors *Pooled results from 4 trials*	***No effect*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No effect*** *(moderate QoE)†*	***Significant risk reduction*** *(moderate QoE)†*

Abbreviations: DPP-4 = dipeptidyl peptidase 4; ER = extended release; GLP-1 RA= glucagon-like peptide 1 receptor agonist; HF = Heart Failure; QoE = quality of evidence; SGLT-2 = sodium-glucose cotransporter-2; XR = extended release
Key: * Evidence was insufficient so no conclusion could be made †Cochrane GRADE methodology[5] was used to determine quality of evidence designation; High – randomized trials or double-upgraded observational studies, Moderate – downgraded randomized trials and upgraded observation studies, Low – double-downgraded randomized trials or observation studies or Very Low – triple-downgraded randomized trials

Severe Adverse Events

Rates of severe adverse events were low for the classes of newer diabetes therapies; however adverse events in general are common with GLP-1 RAs and SGLT-2 inhibitors. Saxagliptin was associated with a greater risk of severe adverse events compared to placebo by 1.8% (number needed to harm [NNH] 56 with a median follow up of 2.1 years).[2] SGLT-2 inhibitors had a significant reduction in risk of severe adverse reactions with canagliflozin, dapagliflozin and empagliflozin compared to placebo, ranging from 2.1% to 4.1%.[2]

There was low quality evidence to suggest GLP-1 RAs had fewer severe adverse reactions compared to placebo.

Limitations

The studies included in the DERP report had limitations that should be considered when applying results to patients with T2DM. The median length of included trials was 2.9 years, which may not have been long enough to sufficiently capture CV outcomes. Multi-site international design of included studies may reduce the generalizability of findings to patients receiving health care in the United States (US). Differences in standards of care may have also influenced the results. External validity is reduced by the inclusion of patients with a 10 year or greater history of diabetes with established CV disease or at high risk of CV disease. There is insufficient evidence on the CV implications of these therapies in patients who are not at high CV risk. Additionally, there were no CV outcome studies that directly compared one newer diabetes therapy to another, so no comparative assessment between drugs or classes could be made.

Dapagliflozin and Heart Failure

Dapagliflozin is the first diabetes therapy to be approved for use in patients without diabetes, as well as those with T2DM, to reduce the risk of CV death and hospitalization for HF in adults with HF with reduced ejection fraction (NYHA class II-IV).[3] Evidence from a phase 3, placebo-controlled, randomized clinical trial demonstrated that dapagliflozin statistically significantly reduced the composite primary outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death compared to placebo (**Table 3**).[4] Comparions among other pre-specified subgroups favored dapagliflozin compared to placebo for the outcomes of hospitalization or an urgent visit for HF (10% vsersus 13.7%) and for CV death (9.6% verus. 11.5%) (p-values not reported).[4] Primary outcome results were similar for patients with and without T2DM. Patients with NYHA class III or IV HF were not found to have a statistically significant benefit from dapagliflozin compared to placebo for the primary endpoint (hazard ratio [HR] 0.90 (95% CI, 0.74 to 1.09; p>0.05).[4] Results are most applicable to the study patient population, which included patients who were at higher risk of hospitalization for HF and CV death compared to other trials and were also on optimized therapy for HF.

Table 3. Dapagliflozin vs. Placebo in Patients with Heart Failure[4]

Comparison	Population	Primary Outcome	Results
Dapagliflozin 10 mg daily **Vs.** **Placebo** **(n=2373)**	Patients with or without diabetes with NYHA class II, III, or IV HF and an ejection fraction of 40% or less	Composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death	Dapagliflozin: 386 (16.3%) Placebo: 502 (21.2%) HR 0.74 (95% CI, 0.65 to 0.85) P<0.001 ARR 4.9% /NNT 21 over a median of 18.2 months

Abbreviations: ARR – absolute risk reduction; CV – cardiovascular; HF – heart failure; HR – hazard ratio; NNT – number needed to treat; NYHA – New York Heart Association

Conclusion

Based on current evidence, patients with T2DM, who are at high risk for CV disease or have established CV disease, may receive some CV benefit from the use of GLP-1 RAs or SGLT-2 inhibitors. Pooled analyses of the class effect of the newer diabetes therapies on the outcomes of stroke or MI risk is of low-to-moderate quality, without definitive evidence of benefit. Lastly, limited evidence suggests that dapagliflozin may have a role in reducing the risk of worsening HF or CV death in patients, with and without T2DM, who have HF with reduced ejection fraction.

For a more comprehensive review of the DERP summary please visit: https://www.orpdl.org/durm/meetings/meetingdocs/2020_08_06/archives/2020_08_06_DM_DERPSummary.pdf

The newer diabetes therapies are recommended second-line after metformin for Oregon Health Plan (OHP) patients. The following medications are preferred for OHP patients:

DPP-4 Inhibitors*
- Saxagliptin
- Sitagliptin
- Sitagliptin/metformin

GLP- Receptor Agonist†
- Exenatide
- Exenatide ER
- Liraglutide
- Dulaglutide

SGLT-2 Inhibitors*
- Dapagliflozin
- Empagliflozin
- Canagliflozin

* Subject to clinical PA criteria
† PA required if not prescribed in conjunction with metformin

Peer Reviewed By:
Nanette Bultemeier, PharmD, BCPS, BC-ADM, CDCES, Clinical Pharmacy Specialist, Providence Medical Group and Tracy Klein, PhD, ARNP, Washington State University Vancouver, Washington

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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: Duchenne Muscular Dystrophy

Date of Review: February 2021

Date of Last Review: June 2020
Dates of Literature Search: 01/01/2020-11/12/2020
Brand Name (Manufacturer): Viltepso® (NS Pharma)
Dossier Received: yes

Generic Name: viltolarsen

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

Purpose for Class Update:
The purpose of this update is to evaluate place in therapy for viltolarsen, a new targeted therapy for Duchenne muscular dystrophy (DMD). Viltolarsen is the second therapy approved for DMD in patients with mutations amenable to exon 53 skipping.

Research Questions:
1. What is the comparative efficacy or effectiveness of therapies for DMD?
2. What is the comparative safety of therapies for DMD?
3. Is viltolarsen safer or more effective than currently available agents for the treatment of patients with DMD?
4. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for DMD?

Summary of Prior Reviews and Current Policy
Therapies FDA approved for treatment of DMD (eteplirsen, golodirsen, and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in June 2020. A previous evaluation of deflazacort found insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions. Evidence was limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients. Current evidence demonstrates no difference in functional outcomes for eteplirsen or golodirsen compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes. Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 5**). Prednisone is available without PA.

Conclusions:
- There is no new comparative efficacy or safety data for golodirsen or eteplirsen. The required post-marketing studies to verify and describe the clinical efficacy of eteplirsen and golodirsen have not yet been completed.

Author: Sarah Servid, PharmD

- A systematic review conducted by the Drug Effectiveness Review Project (DERP) evaluated efficacy and safety of deflazacort compared to prednisone. Four RCTs of poor methodological quality showed insufficient evidence that demonstrated no difference in muscle strength and motor outcomes between deflazacort and prednisone for patients with DMD.[1] Similarly, there is insufficient evidence to evaluate comparative differences in adverse effects between deflazacort and prednisone. Compared to prednisone, deflazacort may be associated with less weight gain but increased risk for cataracts and fractures.[1] Due to significant methodological limitations of these trials and lack of reported data, the true treatment effect is likely to be substantially different from the estimated treatment effect.[1]
- There is insufficient evidence that use of viltolarsen in patients with DMD mutations amenable to exon 53 skipping has any impact on symptoms, muscle or pulmonary function, quality of life, or disease progression. Efficacy trials comparing viltolarsen to placebo have not yet been completed.
- Viltolarsen 80 mg/kg weekly was approved based on a phase 2 trial with high risk of bias, which demonstrated a slight improvement in dystrophin protein over 24 weeks compared to baseline (mean improvement of 5.3% of normal [SD 4.5; 95% CI 3.4 to 7.4]).[2,3] The functionality of the truncated dystrophin protein produced as a result of viltolarsen treatment has not been determined and may vary depending on the type of inherited mutation. It is not known if improvement in dystrophin correlate to clinical outcomes, and there is no consensus on the minimum amount of dystrophin that may result in a clinical improvement.
- There is insufficient evidence regarding long-term safety of viltolarsen. Evidence is limited by the small population of patients which have received viltolarsen. Only 16 patients had been prescribed viltolarsen for more than 12 months prior to approval by the Food and Drug Administration (FDA).[2] Like golidersen, viltolarsen labeling includes warnings for renal adverse events based on data from animal studies. Because viltolarsen is administered intravenously weekly, like other targeted therapies for DMD, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.

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

Background:
Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.[4] In the United States, it's estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,[2,4] and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.[5] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.[4] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which authors attributed to improvements in care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[6] Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.[6] The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.[6]

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.[4,7] Corticosteroids are

often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[4] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.[4] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[4]

Recent new therapies approved for DMD include targeted, exon-skipping therapies. The goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.[8] Therapies are FDA approved for specific mutations that are amenable to exon skipping. Eteplirsen was FDA approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[9] In the past year, golodirsen and, more recently, viltolarsen were FDA approved for patients with mutations amenable to exon 53 skipping. Mutations amenable to exon 53 skipping are thought to represent about 8% of the DMD population (approximately 1200 patients in the United States).[10] Both therapies have the same mechanism of action and are administered as weekly intravenous infusions.

These therapies have been approved based on the surrogate marker of dystrophin protein. While eteplirsen and golodirsen have shown a slight increase in dystrophin (<1% of normal dystrophin levels), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.[11,12] In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test at 24 or 48 weeks compared to placebo. While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.[13-16] Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.[10] Confirmatory post-marketing, randomized trials have yet to be completed for either therapy.

Targeted exon skipping therapies for DMD have been FDA-approved based on a surrogate marker of dystrophin production. It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes, and there is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement. Available thresholds cited in the literature are currently based on expert opinion, and evidence has yet to correlate improved dystrophin levels in patients with DMD with any clinical outcomes. An FDA analysis evaluating the change in 6MWT per year and dystrophin level associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[10] In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[17] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[17] Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[17,18] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[17]

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34). It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2 scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. Other standard timed functional tests include time to climb 4 stairs, time to walk 10

meters, time required to stand from a prone position, and the 6 minute walking test (6MWT) which evaluates distance traveled in 6 minutes. In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[16,19,20] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[21] NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[22] The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes, but score is often very dependent on patient effort.[17] Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).[23,24] However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to thresholds for clinical outcomes such as need for mechanical ventilation or airway clearance.[23]

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 high quality systematic review conducted by the Drug Effectiveness Review Project (DERP) evaluated efficacy and safety of prednisone compared to deflazacort.[1] This systematic review was an update of a 2017 review. In the original review, 4 comparative RCTs were identified. This update identified several new observational studies and one systematic review, but no new RCTs. Evidence from RCTs was significantly limited by poor methodological quality and inconsistency across studies.[1] Limitations included incomplete outcome reporting, high attrition, and unclear randomization and allocation concealment methods.[1] Studies were of generally of small sample size (18 to 196 patients) and of short duration (3 months to 2 years).[1] While deflazacort has an FDA-approved indication for patients at least 2 years of age, trials only included patients over 5 years of age.[1] Evidence for functional outcomes was graded as very low quality indicating no confidence in the direction of effect.[1] One small trial (n=34) reported improved motor function index score with deflazacort compared to prednisone at 18 months (18.1% vs. 15%), but no difference in functional motor outcomes upon follow-up at 24 months.[1] Two trials reported no difference between deflazacort and prednisone in muscle strength from baseline to 3 to 12 months.[1] Similarly, all outcomes pertaining to differences in adverse effects were graded as very low quality due to methodological limitations. Four studies reported less weight gain with deflazacort compared to prednisone. Average differences in weight from baseline are reported in **Table 1**. Two RCTs noted increased risk for cataracts with deflazacort with differences of 6.6% versus 4.4% and 36% versus 3%, respectively.[1]

Table 1. Average weight change from baseline reported in RCTs[1]

Study	Duration	Deflazacort	Prednisone	Statistical reporting
Griggs et al N=196	12 months	5.05 kg; 95% CI, 4.08 to 6.01	8.45 kg; 95% CI, 7.41 to 9.49	P<0.001
Bonifati et al. N=18	12 months 24 months	2.17 kg (variance not reported) 4.6 kg (variance not reported)	5.08 kg (variance not reported) 8.7 kg (variance not reported)	P<0.05 P<0.05
Karimzadeh et al N=34	12 months 18 months	13.0% (variance not reported) 21.7% (variance not reported)	21.7% (variance not reported) 32.0% (variance not reported)	P=0.001 P=0.046
Reitter, 1995; Dubowitz, 2000 N=100	24 months	Not reported	Not reported	Statistical significant difference reported only descriptively

Seven observational trials which compared deflazacort to prednisone were described in the DERP report. All had significant risk for selection bias related to availability of deflazacort compared to prednisone, differences in baseline characteristics between groups, lack of disclosure for study funding, and small sample sizes.[1] For example, several trials had a higher daily doses of deflazacort compared to prednisone dose which may account for some differences between groups.[1] Because of these substantial differences in baseline characteristics between groups, it significantly limits confidence in findings from these studies.

Efficacy Outcomes

- Four trials reported age of ambulatory loss as a functional outcome with inconsistency between studies. Two studies reported no difference between deflazacort and prednisone, and two studies, both evaluating data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) dataset, found improvement in patients treated with deflazacort compared to prednisone by a median of 2.7 years (13.9 vs. 11.2; p< 0.001 and 14.0 ± 0.20 vs. 11.3 ± 0.42; p=0.01).[1]
- Data for other motor function outcomes was mixed not reported consistently for all outcomes across studies.

Safety Outcomes

- Five of the 6 studies evaluating weight gain reported similar changes in weight between groups.[1] Only one trial evaluated statistical differences in weight and found less weight gain associated with deflazacort compared to prednisone.[1] However, in the same study no differences in BMI were observed which authors attributed to a significantly shorter stature in patients treated with deflazacort.[1] This observational data conflicts with differences in weight observed in RCT. However, it is possible that differences in results may be explained by variability in deflazacort and prednisone dose in observational studies, limited statistical analysis of weight-related outcomes, and lack of long-term outcomes in RCTs.[1]
- Of the 4 observational studies evaluating cataracts, 2 identified a statistically significant increased risk of cataracts with deflazacort compared to prednisone (OR 2.4; 95% CI 1.5 to 4.5 and 29% vs. 5%, respectively).[1] Two studies reported numerically higher incidence of cataracts with deflazacort compared to prednisone, though statistical significance was not reported.[1]
- Adverse effects related to growth delay were mixed with 2 studies noting increased risk of growth delay associated with deflazacort compared to prednisone and 2 studies noting no difference between treatments.[1]
- In one retrospective analysis, deflazacort was associated with an evaluated fracture risk compared to prednisone. The time to first fracture was shortest with deflazacort (mean 5.9 years; 95% CI 4.5 to 7.3; *p=0.*03).[1] Overall fracture incidence rate in patients with DMD was 682 per 10000 patient-years (95% CI 579-798) and was highest in patients treated with daily deflazacort (1366.6 per 10000 patient-years; 95% CI 796.1-2188.0).[25]

After review, one systematic review was excluded due to poor quality (e.g., did not meet AMSTAR II criteria).[5]

New Guidelines:
No new high quality guidelines were identified since the last review.

New Formulations or Indications:
No new formulations were identified.

New FDA Safety Alerts:
No new safety alerts were identified.

Randomized Controlled Trials:
A total of 16 citations were manually reviewed from the initial literature search. None of the identified studies met quality inclusion criteria. 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). Key inclusion criteria for RCTs are listed in **Appendix 4**. The phase 2 RCT evaluating efficacy of viltolarsen was included in the new drug evaluation below as it was the primary trial used for FDA-approval.

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:
Viltolarsen 80 mg/kg weekly was FDA-approved for DMD based on a phase 2, dose-finding trial with high risk of bias (**Table 4**).[3] A second phase 2, dose-finding trial conducted in Japan remains unpublished, and data from this study was not used for FDA approval due to lack of adequate methods for dystrophin measurment.[2] The trial used for FDA-approval enrolled 16 patients who were randomized to low (40mg/kg) or high (80mg/kg) dose viltolarsen for 4 weeks.[3] A placebo group was included for safety outcomes only for the first 4 weeks. Patients were enrolled in a 20 week open-label extension phase with either 40 or 80 mg/kg viltolarsen following the randomized 4-week safety period.[3] The study had high risk of bias, primarily due to the lack of placebo comparator and open-label design after 4 weeks. Laboratory outcomes were reported as pre-specified, but results were available for only 3 of the 6 functional outcomes (those that had demonstrated statistical significance). Patients enrolled in the phase 2 trial were ambulatory and able to complete all baseline functional assessments limiting applicability in patients with severe disease.[3]

The primary efficacy outcome was change in dystrophin production evaluated by Western blot analysis.[3] Western blot analysis provides a semi-quantitative assessment of dystrophin production by comparing muscle biopsy samples to a standard curve of dystrophin generated from biopsies collected from a range of patients with varying dystrophin levels (patients with DMD to normal controls). Results are reported as a percent of normal dystrophin levels. At baseline, the mean dystrophin level was 0.6% of normal by Western blot.[2] The primary outcome was supported by analysis of dystrophin using 3 other methods: dystrophin mRNA splicing on reverse transcription-polymerase chain reaction (RT-PCR), dystrophin protein production by mass spectrometry (MS), and dystrophin

localization by immunofluorescence (IF) staining.[3] The FDA recommends that IF staining and RT-PCR be used as qualitative assessments only and are not recommended to make conclusions regarding dose or efficacy.[2] Upon analysis by Western blot at 24 weeks, patients treated with viltolarsen demonstrated a mean improvement in dystrophin from baseline of 5.3% (SD 4.5; 95% CI 3.4 to 7.4) to 5.4% (SD 2.4; 95% CI 1.6 to 9.0%) for patients treated with 80 and 40 mg/kg, respectively.[2,3] FDA approval was for 80 mg/kg weekly. A dose response was not observed with analysis of dystrophin by Western blot, but there was a numerically higher (though not statistically significant) dose response upon analysis by MS (mean difference of 3.7% vs. 1.5% of normal for 80 and 40 mg/kg, respectively, p=0.16 between groups).[2] In general, all secondary analysis methods reported consistent direction of effect with regard to dystrophin production.[2] Patients who demonstrated higher improvement on Western blot analysis also had consistent outcomes when using other analytical methods to evaluate dystrophin levels.[2]

Evaluation of dystrophin in patients treated with golodirsen and eteplirsen resulted in changes in dystrophin of that were less than 1% of normal.[11,26] While viltolarsen had a mean improvement of 5.3% to 5.4% of normal, it is difficult to make comparisons between trials due to differences in populations, genotypes, and variability in methods used for evaluation of dystrophin. For example, it is likely that genotype impacts disease progression and may be a possible factor in dystrophin production for patients amenable to exon 51 versus 53 skipping. In patients amenable to exon 53 skipping, patients enrolled in the trial for golodirsen were slightly older (mean 8.2 years) compared to viltolarsen trials (7.4 years).[3,26]

While a comparison of functional outcomes was performed versus historical controls, use of historical controls in this population has significant limitations and should not be used for evaluation of efficacy. Patients enrolled in the clinical trial were not matched to historical controls and relevant clinical data regarding time and age of diagnosis, corticosteroid dose, ventilator support, cardiac or pulmonary function, and data on other non-pharmacologic therapy was unavailable for historical controls.[3] Additionally, historical control patients had worse mean functional outcomes at baseline including a longer 6MWT, longer time to stand from supine, time to climb 4 stairs, and higher NSAA score.[3] This may be indicative of more severe or symptomatic disease for control patients which may bias results in favor of treatment. These potential confounding factors could have significant impact on disease progression or functional ability which increases risk of bias upon comparison to a historical control. Additional data are needed to confirm clinical benefit.

Similar to other targeted therapies for DMD, the clinical benefit of viltolarsen has yet to be determined. Currently available data indicate no clinical impact on disease progression, and available data are significantly limited by the open-label, non-controlled study design. Functional outcomes can be susceptible to expectation bias and coaching which significantly confounds the benefit when compared to historical disease progression. Additionally, it is unclear whether improvements in dystrophin correlate to clinical outcomes. There is currently no consensus on what difference in dystrophin may be clinically significant.

Clinical Safety:
At the time of FDA approval there were 32 patients exposed to viltolarsen, 16 of which had been on treatment for more 12 months.[2] During clinical trials there were no deaths, no discontinuations due to adverse events and only 2 patients experienced severe adverse events (respiratory tract infection and limb fracture).[2] The most common adverse events were upper respiratory infections, injection site reactions, cough, and pyrexia (**Table 2**).

Table 2. Adverse events occurring in more than 10% of patients receiving viltolarsen 80 mg/kg.[27]

Adverse event	Viltolarsen 80 mg/kg weekly (n=16)
Upper respiratory tract infection	10 (63%)
Injection site reaction	4 (25%)
Cough	3 (19%)
Pyrexia	3 (19%)
Contusion	2 (13%)
Arthralgia	2 (13%)
Diarrhea	2 (13%)
Vomiting	2 (13%)
Abdominal pain	2 (13%)
Ejection fraction decreased	2 (13%)
Urticaria	2 (13%)

Because viltolarsen is administered intravenously weekly, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.[2] This concern was first noted in an FDA review of post-marketing adverse events for eteplirsen and is a potential risk for all weekly intravenous treatments for DMD. In addition, like other oligonucleotide therapies for DMD, pre-clinical animal studies identified a potential risk for serious renal adverse events. While no renal adverse events were documented in clinical trials, renal monitoring is recommended prior to and during viltolarsen therapy.[27] Because serum creatinine may not accurately reflect renal function in patients with DMD, labeling recommendations include serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio.[27] If persistent changes are noted, a referral to a pediatric nephrologist is recommended.

In the available clinical studies, only one patient (6.25%) was identified with anti-drug antibodies.[2] However, due to the sensitivity of the test used, false negatives could not be ruled out, and a post-marketing trial with improved sensitivity is required to validate these results.[2] Additional post-marketing requirements include an assessment of viltolarsen on QT prolongation, animal carcinogenicity studies, a placebo controlled trial over 48 weeks to establish efficacy (primary endpoint planned as time to stand), and surveillance for serious renal adverse events.[2]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
2) Quality of life
3) Disease progression
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Efficacy Endpoint:
1) Dystrophin protein production

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Viltolersen binds to Exon 53 of the dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and producing an internally truncated dystrophin protein
Oral Bioavailability	N/A (administered intravenously)
Distribution and Protein Binding	Vd = 0.3 L/kg at FDA approved dose (80mg/kg) 39-40% protein binding
Elimination	Excreted unchanged in the urine
Half-Life	2.5 hours
Metabolism	N/A

Abbreviations: kg= kilograms; L=liters; N/A = not applicable; Vd = volume of distribution

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.Clemens, et al. 2020.[3] FDA Summary Review[2] Phase 2, open-label, dose-comparison, MC, RCT	1. viltolarsen 80 mg/kg weekly 2. viltolarsen 40 mg/kg weekly 3. placebo 4 weeks Following 4 weeks participants were enrolled in a 20-week open label extension. Patients originally randomized to placebo were switched to viltolarsen.	Demographics: - Age: 7.4 yrs (SD 1.8) - White: 94% - BMI: 17.4-17.9 kg/m^2 - Time to run/walk 10 m: 5.93 s (SD 1.47) - Time to stand from supine: 4.44 s (SD 1.96) - 6MWT: 372.4 m (SD 78.6) - Time to climb 4 stairs: 3.61 s (SD 0.95) - NSAA: 24.3 (SD 5.4) Key Inclusion Criteria: - Age 4-9 yrs - DMD amenable to exon 53 skipping - Normal labs - Ambulatory without assistive devices - Able to complete baseline functional assessments - Stable steroid dose in prior 3 months Key Exclusion Criteria: - Acute illness 4 weeks before enrollment* - Symptomatic cardiomyopathy - Severe behavioral or cognitive problems - Surgery in prior 3 mo - HBV, HCV, HIV - Other medical findings which would impair assessment of study results or safety* *as assessed by site investigator	Part 1: ITT 1. 6 2. 6 3. 4 PP 1. 6 2. 5 3. 5 Part 2 1. 8 2. 8 Attrition 1. 0 2. 0	Primary Endpoint: Dystrophin production (by Western blot) at 24 wks 1. 5.9% (SD 4.5%); change from baseline: 5.3% (SD 4.5%); 95% CI 3.4 to 7.4% 2. 5.7% (SD 2.4%); change from baseline: 5.4% (SD 2.4%); 95% CI 1.6 to 9.0% Secondary Endpoints: Outcomes for functional assessments were reported graphically or at 25 weeks compared to historical control and should not be used to establish efficacy. Measures of variance were reported only graphically. Mean change in time to stand from supine Viltolarsen: -0.19s Historical Control: 0.74s P=0.04 * when evaluated as velocity results were NR with NS difference from historical controls Change in time to travel 10m (velocity) Viltolarsen: 0.23m/s Historical Control: -0.04m/s P=0.003 Change in time to travel 10m (reported graphically; results are approximate) Viltolarsen: -0.6s Historical control: 0.1s p=0.046 Change in time to climb 4 stairs, NSAA, and muscle strength not reported Difference from historical control: NS Change in 6MWT from baseline (25 wks) Viltolarsen: 28.9 m Historical control: -65.3 m P=0.047	NA for all	SAE 0% DC due to AE: 0% TEAE 1. 4 (67%) 2. 4 (80%) 3. 3 (60%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Method of randomization not reported; no allocation concealment. An unblinded statistician performed randomization based on a permuted block design. Performance Bias: High. Open-label design without placebo comparison for all outcomes after 4 weeks. Lack of blinding increases risk of bias for effort-based functional assessments. Detection Bias: High. Laboratory assessors blinded to treatment group. Blinding of sample type (before vs. after therapy) was NR. Attrition Bias: Low. One patient randomized to vilitolarsen but received placebo for 4 weeks. All patients completed 24 weeks of treatment. Reporting Bias: Unclear. Primary results reported as specified. Results available for only 3 of 6 functional outcomes. No multiplicity testing for multiple outcomes. Other Bias: Unclear. Manufacturer was involved in study design; collection, management, analysis and interpretation of data; and preparation and review of the paper. **Applicability**: Patient: Patients were ambulatory and able to complete all baseline functional assessments. Patients with acute illness or cardiomyopathy were excluded limiting applicability in patients with severe disease. Baseline pulmonary function was not reported. Intervention: Intervention given as a 2nd line therapy to corticosteroids. Functional outcomes were not reported by dose and no dose response was observed upon analysis of dystrophin production by Western blot. Upon analysis by MS, there was a slightly higher (though not significant) improvement in dystrophin production with the FDA approved dose of 80 mg/kg compared to 40 mg/kg (3.7% vs. 1.5% of normal, respectively, p=0.16). Comparator: Lack of control group after 4 weeks limits conclusions regarding efficacy of treatment or long-term safety. Functional outcomes compared to historical control. No patient to patient matching occurred for historical control and important markers of disease progression were not reported including steroid dose, pulmonary function, and non-pharmacological therapy (e.g., physical therapy, assistive devices, ventilator support, etc).

								Outcomes: Primary outcome is a surrogate marker and correlation of functional outcomes with dystrophin levels is unclear. There is no agreement on what level of dystrophin may result in a clinically important difference. Setting: 5 sites in the United States and 1 site in Canada from December 2016 to August 2017.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; BMI = body mass index CI = confidence interval; DC = discontinuation; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; ITT = intention to treat; MC = multicenter; mo = months; MS = mass spectrometry; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; NSAA = North Star Ambulatory Assessment; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; TEAE = treatment-emergent adverse events; wks = weeks; yrs = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route
deflazacort	EMFLAZA	ORAL SUSP	PO
deflazacort	EMFLAZA	TABLET	PO
eteplirsen	EXONDYS-51	VIAL	IV
golodirsen	VYONDYS-53	VIAL	IV
viltolarsen	VILTEPSO	VIAL	IV

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 11, 2020

1	exp Muscular Dystrophy, Duchenne/	5572
2	limit 1 to (english language and humans)	4118
3	limit 2 to yr="2020"	95
4	limit 3 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	16

Appendix 3: Prescribing Information Highlights

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

VILTEPSO (viltolarsen) injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
VILTEPSO is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILTEPSO. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------
- Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting VILTEPSO. (2.1)
- Recommended dosage is 80 milligrams per kilogram of body weight once weekly. (2.2)
- Administer as an intravenous infusion over 60 minutes. (2.2, 2.4)
- If the volume of VILTEPSO required is less than 100 mL, dilution in 0.9% Sodium Chloride Injection, USP, is required. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 250 mg/5 mL (50 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.1, 13.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥15% in patients treated with VILTEPSO) were upper respiratory tract infection, injection site reaction, cough, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NS Pharma at 1-866 NSPHARM (1-866-677-4276) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with Duchenne Muscular Dystrophy
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Function, symptoms, disease progression, quality of life, morbidity, mortality
Timing	Any duration
Setting	Outpatient

Drugs for Duchenne Muscular Dystrophy

Goal(s):

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

Length of Authorization:

- 6 months

Requires PA:

- Targeted therapies for exon skipping (pharmacy or physician administered claims)
- Deflazacort

Covered Alternatives:

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

Table 1. FDA Approved Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58
Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

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

Approval Criteria		
~~2. Is the drug being used to treat an OHP-funded condition?~~	~~**Yes:** Go to #3~~	~~**No:** Pass to RPh. Deny; not funded by the OHP.~~
~~3.~~2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: ~~Eteplirsen, golodirsen, and deflazacort~~Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
~~Is the request for continuation of treatment?~~	~~**Yes:** Go to **Renewal Criteria**~~	~~**No:** Go to #5~~
~~4.~~3. Is the request for deflazacort?	**Yes:** Go to #4	**No:** Go to #7
~~5.~~4. Is the patient ≥ 2 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
~~6.~~5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~7.~~6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.
7. Is the request for continuation of treatment previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8
8. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
~~10.~~11. Has the provider assessed baseline renal function as recommended in the FDA label? Golodirsen: documented glomerular filtration rate as evaluated by a 24 hour urine collection within the past 3 months Viltolarsen: Serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
~~11.~~12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~12.~~13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #2	**No:** Go to #3
2. Has the provider assessed renal function? Golodirsen: Recommended monitoring includes proteinuria monthly and serum cystatin C every three months. If results are abnormal, a 24H urine collection should be performed. Viltolarsen: Recommended monitoring includes urine dipstick monthly, serium cyctatin C every 3 months, and protein-to-creatine ratio every 3 months.	**Yes:** Go to #3	**No:** Pass to RPh, Deny; medical appropriateness.
3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Go to #4 Document functional status and provider attestation.	**No:** Pass to RPh, Deny; medical appropriateness.
4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?	**Yes:** Go to #5	**No:** Approve for up to 6 months
5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?	**Yes:** Approve for up to 6 months Document provider attestation	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *2/21 (SS); 6/20; 09/19; 11/17; 07/17*
Implementation: *7/1/20; 11/1/19; 1/1/18; 9/1/17*

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: Acne Drugs

Date of Review: February 2021

Date of Last Review: June 2020
Dates of Literature Search: 12/26/2019 - 12/01/2020
Brand Name (Manufacturer): Winlevi (Cassiopea, Inc.)
Dossier Received: yes

Generic Name: Clascoterone Cream

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

Purpose for Class Update:
The acne class has had one new approval, clascoterone cream, since it was last reviewed in 2019. The purpose of this update is to evaluate new comparative evidence for clascoterone cream for the treatment of acne vulgaris and any new data on comparative efficacy or harms in the acne class since the previous update. Acne conglobata, acne fulminans, and severe cystic acne are covered conditions under the Oregon Health Plan (OHP).

Research Questions:
1. What is the comparative efficacy and effectiveness of treatments for severe acne (**Appendix 1**; hormonal agents of oral contraceptives and spironolactone; clascoterone)?
2. What are the comparative harms of treatments for severe acne?
3. Are there subpopulations of patients in which a particular treatment for severe acne would be more effective or associated with less harm?

Conclusions:
- Recent Cochrane reviews evaluating azelaic acid and topical benzoyl peroxide support current policy.[1,2]
- Clascoterone was evaluated versus a placebo vehicle in moderate to severe acne in two fair quality trials.[3] Quality is limited by risk of bias (RoB) related to industry funding. Applicability is limited by lack of long-term data, lack of racial diversity in study population, and limitations related to placebo control rather than active control.
    - Clascoterone was superior versus vehicle for treatment success (Investigator's Global Assessment [IGA] scale minimum 2-point improvement from baseline AND a score of 0 [clear] or 1 [almost clear]; this is considered a clinically meaningful endpoint) at twelve weeks based on moderate quality evidence (study 1; 16.1% clascoterone patients vs. 7.0% vehicle patients, RR 2.3, 95% confidence interval [CI] 1.4 to 3.8, p<0.001, number needed to treat [NNT] 11; study 2; 18.7% clascoterone patients vs 4.7% vehicle patients, RR 3.7, 95% CI 2.2 to 6.3, p<0.001, NNT 8).
    - Clascoterone was superior versus vehicle for absolute change in non-inflammatory lesion count (NILC) at 12 weeks (study 1; Lesion count difference -6.4, 95% CI -10.3 to -2.6, p<0.001; study 2; lesion count difference -8.6, 95% CI -12.3 to -4.9, p<0.001). (moderate quality evidence)

Author: Sara Fletcher, PharmD, MPH, BCPS

- Clascoterone was superior versus vehicle for absolute change in inflammatory lesion count (ILC) at 12 weeks (study 1; lesion count difference -3.8, 95% CI -6.4 to -1.3, p=0.003; study 2; lesion count difference -7.4, 95% CI -9.8 to -5.1, p<0.001). (moderate quality evidence)

- Clascoterone has similar rates of local skin reactions (LSR) and treatment emergent adverse events (TEAE) compared to vehicle. Safety in pregnancy and risk of Hypothalamic-Pituitary-Adrenal (HPA) axis suppression with long-term use are unknown.

Recommendations:

- Designate clascoterone as non-preferred on Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan (PMDP).
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

- Two high quality systematic reviews evaluated comparative efficacy and safety of oral isotretinoin with other acne vulgaris treatments. These reviews contain low- and very low-quality evidence due to various biases and methodological study limitations.
- Trifarotene has moderate quality evidence due to study limitations to support its use in moderate acne vulgaris. Quality is limited by unclear selection bias, high attrition bias, and bias related to industry funding. Applicability is limited by lack of racial diversity in study population and limitations related to placebo control rather than active control. Number needed to treat of 6 to 10 for treatment success as defined by trial protocol.
- With the exception of oral isotretinoin, there is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Multiple therapies including topical and systemic products are used for the treatment of severe acne. Currently, trifarotene cream and other new single-source brand formulations are non-preferred on the preferred drug list (PDL) given lack of high-quality data to support use in severe acne.
- Prior authorization (PA) criteria for the Acne preferred drug list (PDL) class includes federal legend topical medications that have FDA approval and an OHA-funded indication for severe acne vulgaris and oral isotretinoin. Use is limited to funded conditions in the OHP **(Appendix 6)**.

Background:

Acne vulgaris (AV) is a chronic skin condition that affects approximately 50 million people in the United States.[4] It most commonly affects adolescents and young adults, but can continue into adulthood. Morbidity associated with acne can include permanent scarring, poor self-image, depression, and anxiety.[4] Acne vulgaris is characterized by noninflammatory open or closed comedones and inflammatory lesions.[5] These are generally located on the face, neck, back, chest, and upper arms.[5,6] Follicular hyperkeratinization, microbial colonization with *Cutibacterium acnes* (formerly *Propionibacterium acnes*), sebum production, and inflammatory factors involving innate and acquired immunity are all involved in the pathology of this condition.[4,5]

Acne conglobata and acne fulminans are two forms of severe acne. Acne conglobata is a severe form of nodular acne that involves recurrent abscesses and communicating sinuses and often results in disfiguring scars.[6] Acne fulminans is a severe variant of inflammatory acne that presents with severe ulceration and occasionally the systemic symptoms of fever and arthralgia.[6] Assessment is done by physical exam and includes a pattern-diagnosis system that evaluates not only the presence and frequency of certain lesions, but also complications such as drainage, hemorrhage, pain and other factors like occupational disability, psychosocial impact, and failure of response to previous therapies.[6]

Treatment for acne may include a variety of agents such as topical medications (i.e., retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic or topical antibiotics (i.e., doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim, dapsone), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.[4,5,7] Choice of treatment depends on severity of disease. Isotretinoin, which has an associated iPLEDGE REMS program, is specifically FDA-approved for severe recalcitrant nodular acne and recommended for severe acne.[5,7] Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.[5,7] These classes of medications are well-established and all have been FDA-approved for many years.

In clinical trials, patients are often described at baseline by Fitzpatrick skin phototypes. This system separates patients into 6 categories (I to VI) based on 2 components: skin tone when unexposed to sunlight and skin reaction to sunlight (e.g., burning and tanning).[7] Increasing Fitzpatrick numbers indicate a darker unexposed skin tone and increasing ability to tan with decreasing risk of burning during sun exposure.[7]

Clinically meaningful outcomes for acne assessment include quality of life (QoL) and symptom reduction as demonstrated by decreased lesion counts or lessened acne severity. While there is no universal grading system, and as many as 18 different grading scales are used in the literature, classification of acne is commonly described as mild, moderate, or severe.[4,6,8] These are delineated by frequency of papules or pustules and presence and frequency of nodules, as well as presence of hyperpigmentation and erythema.[6] The Physician's Global Assessment (PGA) is a 5-point scale (0-4) that was previously recommended by the Food and Drug Administration (FDA) to evaluate success in clinical trials of acne vulgaris treatment.[9] The scale defines the skin as clear, almost clear, mild, moderate, and severe with corresponding descriptions for each score based on number of comedones, papules, pustules, nodules, cysts and overall amount of face involved.[9] More recently, the FDA has given industry guidance to use the Investigator's Global Assessment (IGA) as an ordinal scale to assess overall severity.[10] The IGA is a 5- or 6-point scale (0-5) that grades hyperpigmentation and erythema as clear, almost clear, mild, moderate, severe, and very severe.[10] It should be used in conjunction with separate counting of inflammatory and noninflammatory lesions.[10] Though there seems to be no universally determined minimal clinically important difference for these outcomes, a consensus view of the authors of the European Evidence-Based Guidelines for Treatment of Acne suggested a minimal clinically important difference of 10% or greater reduction in lesion count as an efficacy outcome.[11] A final IGA assessment of 0 to 1 (clear to almost clear) and at least a 2-grade improvement from baseline is defined by the FDA as a clinically meaningful outcome.[10]

There are no QoL assessment tools recommended in the FDA guidance to industry[10], nor was it included in the current new drug evaluation. Development and validation of a patient reported outcome measure for assessing acne treatment in the clinic is an identified research gap.[4]

Table 1: Acne class patient claims from second quarter 2020

PDL status of initial medication claim	Patients with claims	Patients with paid claims for the requested medication or another within class within 90 days	Patients with denied claims
Preferred	361	55 (15%)	306 (85%)
Non-preferred	16	0	16 (100%)

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

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

Systematic Reviews:
After review, 4 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).[12-15]

Cochrane-Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and fruit acid (alpha-hydroxy acid) for acne
The effects of various topical treatments for acne when compared to other topical treatments, placebo, or no treatment were assessed through May 2019.[1] Forty-nine randomized controlled trials (RCT) (n=3880) of ages 10-45 years with primarily female participants were included.[1] Of trials where severity was reported (n=2939), 75.7% had mild to moderate acne, the remaining had a mix severities with at least 334 patients having moderate, severe, or severe cystic acne.[1] Treatment duration was over 8 weeks for 59% of the included RCTs.[1] There were 26 RCT with high RoB in at least one domain, while most domains were low or unclear RoB.[1] Azelaic acid is the only agent on the OHP PMDP that will be reviewed here.

The primary outcome was participant's global self-assessment of acne improvement.[1] Azelaic acid is probably less effective than benzoyl peroxide (BPO) (risk ratio [RR] 0.82, 95% CI 0.72 to 0.95; 1 study, n=351, moderate-quality evidence).[1] There is likely no or minimal difference between azelaic acid and tretinoin (RR 0.94, 95% CI 0.78 to 1.14; 1 study, n=289, moderate-quality evidence) and azelaic acid and clindamycin (RR 1.13, 95% CI 0.92 to 1.38; 1 study, n=229, low-quality evidence).[1] There is uncertainty regarding any difference between azelaic acid and adapalene (1 study, n=55, very low-quality evidence).[1]

Safety differences defined as total minor adverse events are unclear between azelaic acid and adapalene (1 study, n=55, very low-quality evidence) and benzoyl peroxide (1 study, n=30, very low-quality evidence).[1] There is no difference when compared to clindamycin (RR 1.5, 95% 0.67 to 3.35, 1 study, n=11, low-quality evidence).[1]

Cochrane-Topical benzoyl peroxide for acne
The effects of topical BPO monotherapy or in combination for acne on the face or trunk was assessed through February 2019.[2] One-hundred and twenty trials (n=29,592) were included.[2] Participants had a mean age of 18 to 30 years, 72 trials included participants with mild to moderate acne and 26 included participants with severe acne.[2] The treatment duration was up to 12 weeks in 108 trials, and high or unclear RoB was common for performance, detection, or attrition bias.[2]

The participant's global self-assessment of acne improvement and withdrawal due to adverse events were the primary outcome measures. BPO may be more effective than placebo or no treatment during 10 to 12 weeks of treatment (RR 1.27, 95% CI 1.12 to 1.45, 3 studies, n=2234, low-certainty evidence).[2] There is minimal to no difference between BPO and adapalene during 11 to 12 weeks of treatment (RR 0.99, 95% CI 0.90 to 1.10, 5 studies, n=1472, low-certainty evidence) and clindamycin during 10 weeks of treatment (RR 0.95, 95% 0.68 to 1.34, 1 study, n=240, low-certainty evidence).[2] Treatment discontinuation over 10 to 12 week treatment durations may be higher with BPO than placebo or no treatment (RR 2.13, 95% CI 1.55 to 2.93, 24 studies, n=13,744, low-certainty evidence).[2] Reasons for discontinuation were erythema, pruritus, and skin burning.[2] Only very low-certainty evidence is available for withdrawal due to adverse events of BPO when compared to adapalene, clindamycin, erythromycin, and salicylic acid.[2] None of these comparisons were statistically significant.[2]

New Guidelines:
No new guidelines were identified for review.

New Formulations or Indications:
None

New FDA Safety Alerts:
None

Randomized Controlled Trials:
A total of 27 citations were manually reviewed from the initial literature search.[16-42] After further review, 27 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 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:
Clascoterone is the first androgen receptor antagonist approved for the topical treatment of acne vulgaris in patients 12 years and older.[43]

Clascoterone has been evaluated in two phase 3, randomized, multicenter, parallel group, double-blind, vehicle-controlled trials of identical design to assess use for the treatment of moderate to severe facial acne vulgaris [Study 1 (NCT 02608450), Study 2 (NCT02608476)].[3,44-46] Patients 9 years of age and older were treated for up to 12 weeks with twice daily clascoterone 1% cream or a placebo vehicle cream. Patients were required to have been on a consistent skincare program for one month prior to, and for the duration of the study. Efficacy was assessed by a 5-point IGA for face in patients with a baseline score of 3 (moderate) or 4 (severe). The IGA is a static evaluation recommended by the FDA for acne severity. FDA guidance recommends limiting efficacy assessment to the face, as it is the most frequent site of involvement.[10] The primary endpoint of treatment success required IGA scale minimum 2-point improvement from baseline AND a score of 0 (clear) or 1 (almost clear). Reduction of ILC and NILC are additional primary endpoints. Secondary endpoints were a reduction of total lesion count (TLC) and percentage change of ILC, NILC, and TLC.[3]

All primary and secondary endpoints are statistically significant in favor of clascoterone for both studies. Success at twelve weeks occurred in 16.1-18.7% clascoterone patients and 4.7-7.0% of vehicle patients (study 1; RR 2.3, 95% CI 1.4 to 3.8, p<0.001; study 2; RR 3.7, 95% CI 2.2 to 6.3, p<0.001). Absolute change in lesion count was greater for clascoterone than vehicle for NILC by an average of -6.4 and -8.6 lesions, ILC by -3.8 and -7.4 lesions, and TLC by -10.3 and -16.4 lesions.[3] See **Table 4** for full results.

Limitations for both of these studies include short duration of therapy of 12 weeks, limited applicability outside of a white patient population, and a significant attrition rate without known cause. Additionally, while statistically significant compared to placebo, the overall success rates were quite low at 16.1% and 18.7%. Given the number of other acne therapies already available, comparison against an active comparator would likely have been more appropriate. There is potential risk of bias from industry involvement in all aspects of the study process.

Clinical Safety:
Clascoterone cream had a similar overall rate of treatment emergent adverse events (TEAE) compared to vehicle (11.3% and 11.4% vs. 11.5% and 13.8%)(**Table 4**).[3] LSR were reported separately from TEAE and were similar between clascoterone and placebo (**Table 2**).[43] In a 9-month open label extension study, the overall frequency of any LSR remained similar rather than dissipating with time.[47] Pregnant women were excluded from these studies. Animal data using supratherapeutic systemic doses of clascoterone show higher rates of malformations and pregnancy loss.[43,45,46] Safety in pregnancy in unknown. Systemic absorption following 14 days of topical application of clascoterone has resulted in HPA axis suppression in 5% of adults and 9% of adolescents (**Table 3**).[43] Long-term risks associated with HPA axis suppression from clascoterone, particularly in the adolescent population, are unknown.

Table 2. New or Worsening Local Skin Reactions[43]

	Clascoterone 1% cream N=674	**Vehicle cream N=656**
Edema	24 (3.6%)	23 (3.5%)
Erythema	82 (12.2%)	101 (15.4%)
Pruritis	52 (7.7%)	54 (8.2%)
Scaling/dryness	71 (10.5%)	68 (10.4%)
Skin atrophy	11 (1.6%)	17 (2.6%)
Stinging/burning	28 (4.2%)	28 (4.3%)
Striae rubrae	17 (2.5%)	10 (1.5%)
Telangiectasia	8 (1.2%)	12 (1.8%)

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Acne severity
2) Number of inflammatory lesions
3) Number of non-inflammatory lesions
4) Quality of Life
5) Serious adverse events

Primary Study Endpoint:
1) IGA reduction (severity)
2) Reduction in inflammatory lesions
3) Reduction in non-inflammatory lesions

6) Study withdrawal due to an adverse event

Table 3. Pharmacology and Pharmacokinetic Properties.[43]

Parameter	
Mechanism of Action	• Androgen receptor inhibitor • Exact mechanism for treatment of acne vulgaris is unknown
Systemic absorption	• Steady state achieved by day 5 • Day 14 Mean ± SD maximum plasma concentration 4.5 ± 2.9 ng/mL • Day 14 HPA axis suppression observed in 5% (1/20) of adults and 9% (2/22) of adolescents. All returned to normal 4 weeks after end of treatment
Distribution and Protein Binding	84% to 89% plasma protein binding
Elimination	• Primary metabolite cortexolone with other possible unidentified metabolites • Excretion not fully characterized
Half-Life	Not reported
Metabolism	Low level inhibition of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 with no expected effect on other substrates

Abbreviations: CYP = cytochrome p450 enzymes; HPA = Hypothalamic-Pituitary-Adrenal; SD = Standard deviation

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. Study 1 NCT 02608450[3,44,45] CB-03-01/25 Phase 3, DB, VC, RCT	1. Clascoterone 1% cream twice daily x 12 weeks 2. Vehicle cream twice daily x 12 weeks Randomized 1:1 Visit at baseline, week 4, week 8, and week 12. Open-label extension planned for additional 9 months	Demographics: Male: 38.4% Median age: 18.0 years Race White: 84.0% Black: 9.7% Asian: 2.7% Fitzpatrick skin type Type I: 2.0% Type II: 31.4% Type III: 34.3% Type IV: 17.9% Type V: 7.1% Type VI: 7.3% Baseline IGA 3 (moderate): 82.3% 4 (severe): 17.7% TLC [mean (SD)] 1. 101.5 (25.12) 2. 103.6 (26.13) NILC [mean (SD)] 1. 59.1 (22.19) 2. 60.7 (22.09) ILC [mean (SD)] 1. 42.4 (11.77) 2. 42.9 (12.31) Key Inclusion Criteria: -Male and non-pregnant females -9 years or older -Moderate to Severe facial acne vulgaris (IGA grade 3 or 4) -30 to 75 ILC -30 to 100 NILC -consistent skincare program 1 month prior to enrollment & for duration of study Key Exclusion Criteria: -more than 2 facial nodules -nodulocystic acne -current use of any OTC or Rx topical (facial) or systemic antiacne product	ITT: 1. 353 2. 355 PP: 1. 270 2. 260 Attrition: 1. 66 (18.7%) 2. 65 (18.3%)	Primary Endpoint: Treatment success: ≥2 point IGA reduction AND score of 0 or 1 (week 12) 1. 57 (16.1%) 2. 25 (7.0%) Point estimate 2.3 (95% CI, 1.4 to 3.8) P<0.001 Treatment success adjusted proportions for missing data: 1. 18.4% 2. 9.0% Change in NILC (baseline to week 12) 1. -19.4 2. -13.0 Difference -6.4 (95% CI -10.3 to -2.6) P<0.001 Change in ILC (baseline to week 12) 1. -19.3 2. -15.5 Difference -3.8 (95% CI -6.4 to -1.3) P<0.003 Secondary Endpoints: Change in TLC (baseline to week 12) 1. -39.1 2. -28.8 Difference -10.3 (95% CI -15.7 to -4.9) P<0.001	9.1% /11	Outcome TEAE : 1. 40 (11.3%) 2. 41 (11.5%) Severe TEAE: 1. 0 2. 2 (0.6%) Study discontinuation due to TEAE: 1. 3 (0.8%) 2. 4 (1.1%) Most frequent TEAE: Nasopharyngitis 1. 6 (1.7%) 2. 13 (3.7%) Headache 1. 2 (0.6%) 2. 1 (0.3%) Oropharyngeal pain 1. 2 (0.6%) 2. 1 (0.3%) Vomiting 1. 2 (0.6%) 2. 2 (0.6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomization via Datatrak One software, permuted block design, block size 4. Blinding of clinical team, patients, investigators, monitors, employees of study site. Performance Bias: (low) Vehicle cream identical to active cream in color, consistency, and smell. Both were packaged in identical blinded tubes. Detection Bias: (low) Lesion count, IGE, adverse events, and LSR assessed at each visit by same investigator (when possible). Attrition Bias: (low) Missing primary endpoint data imputation by: multiple imputation using missing at random assumption, missing at worst value (for entire set), worst case, LOCF, and baseline observation carried forward. Large number LTFU in both groups. Reporting Bias: (low) Roughly ½ of attrition was for "withdrawal" without reason stated. LSR not presented in safety results table. Other Bias: (high) Industry sponsor Cassiopea SpA responsible for funding, preparation, review, approval, and publication submission of manuscript and study collection, management, analysis, data interpretation. **Applicability**: Patient: Patients predominantly white and with Fitzpatrick skin type II or III (of VI), limiting applicability to other skin types (e.g. African Americans or Latinos). Only 18% had severe acne. Intervention: Intervention appropriate with consistent skincare routine. Comparator: Placebo appropriate, but comparison with active comparator would enable comparative assessment of clinical efficacy. Outcomes: IGA and lesion count are common outcomes in acne assessment.

		-women on COC for non-acne indications must be on tx x 12 weeks prior to study and remain on same product & dose throughout -Systemic CS not allowed within 4 weeks, non-systemic CS (inhaled, intranasal, ocular) require stable dose x 4 weeks -light treatments, microdermabrasion, or chemical peels within 8 weeks						Setting: 45 sites in US, 7 sites in Ukraine, 3 sites in Republic of Georgia
2. Study 2 NCT 02608476[3,44,46] CB-03-01/26 Phase 3, DB, VC, RCT	See Study 1	Demographics: Male: 36.6% Median age: 18.0 years Race White: 96.3% Black: 1.8% Asian: 0.5% Fitzpatrick skin type Type I: 2.6% Type II: 31.3% Type III: 45.9% Type IV: 15.2% Type V: 3.8% Type VI: 1.2% Baseline IGA 3 (moderate): 84.4% 4 (severe): 15.6% TLC [mean (SD)] 1. 105.7 (25.76) 2. 104.6 (24.18) NILC [mean (SD)] 1. 62.8 (21.37) 2. 63.3 (20.52) ILC [mean (SD)] 1. 42.9 (12.20) 2. 41.3 (10.96) Key Inclusion Criteria: See Study 1 Key Exclusion Criteria: See Study 1	ITT: 1. 369 2. 363 PP: 1. 286 2. 268 Attrition: 1. 67 (18.2%) 2. 81 (22.3%)	Primary Endpoint: Treatment success: ≥2 point IGA reduction AND score of 0 or 1 (week 12) 1. 69 (18.7%) 2. 17 (4.7%) Point estimate 3.7 (95% CI, 2.2 to 6.3) P<0.001 Treatment success adjusted proportions for missing data: 1. 20.3% 2. 6.5% Change in NILC (baseline to week 12) 1. -19.4 2. -10.8 Difference -8.6 (95% CI -12.3 to -4.9) P<0.001 Change in ILC (baseline to week 12) 1. -20.0 2. -12.6 Difference -7.4 (95% CI -9.8 to -5.1) P<0.001 Secondary Endpoints: Change in TLC (baseline to week 12)	14%/ 8	TEAE: 1. 42 (11.4%) 2. 50 (13.8%) Severe TEAE: 1. 0 2. 1 (0.3%) Study discontinuation due to TEAE: 1. 2 (0.5%) 2. 8 (2.2%) Most frequent TEAE: Nasopharyngitis 1. 4 (1.1%) 2. 7 (1.9%) Headache 1. 4 (1.1%) 2. 3 (0.8%) Oropharyngeal pain 1. 4 (1.1%) 2. 4 (1.1%) Vomiting 1. 2 (0.5%) 2. 1 (0.3%)	NA	**Risk of Bias (low/high/unclear)**: See study 1 **Applicability**: Patient: See study 1 Intervention: See study 1 Comparator: See study 1 Outcomes: See study 1 Setting: 10 sites in US, 8 sites in Bulgaria, 9 sites in Romania, 12 sites in Poland, 3 sites in Serbia, 6 sites in Republic of Georgia

				1. -40.0 2. -23.6 Difference -16.4 (95% CI -21.8 to -11.0) P<0.001				

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; COC = combined oral contraceptives; CS = corticosteroids; DB = double-blind; IGA = Investigator's Global assessment; ILC = inflammatory lesion count; ITT = intention to treat; LOCF = last observation carried forward; LSR = local skin reaction; LTFU = lost to follow-up; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NILC = non-inflammatory lesion count; NNH = number needed to harm; NNT = number needed to treat; OTC = over-the-counter; PP = per protocol; RCT = randomized controlled trial; Rx = prescription; SD = standard deviation; TEAE = treatment emergent adverse event; TLC = total lesion count; tx = treatment; US = United States; VC = vehicle-controlled

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47. Eichenfield L, Hebert A, Gold LS, et al. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. J Am Acad Dermatol 2020;83:477-85.

Generic	Brand	Route	Form	PDL
adapalene	ADAPALENE	TOPICAL	CREAM (G)	Y
adapalene	DIFFERIN	TOPICAL	CREAM (G)	Y
adapalene	ADAPALENE	TOPICAL	GEL (GRAM)	Y
adapalene	DIFFERIN	TOPICAL	GEL (GRAM)	Y
adapalene	ADAPALENE	TOPICAL	GEL W/PUMP	Y
adapalene	DIFFERIN	TOPICAL	GEL W/PUMP	Y
adapalene	DIFFERIN	TOPICAL	LOTION	Y
adapalene/benzoyl peroxide	ADAPALENE-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y
adapalene/benzoyl peroxide	EPIDUO	TOPICAL	GEL W/PUMP	Y
azelaic acid	AZELAIC ACID	TOPICAL	GEL (GRAM)	Y
azelaic acid	FINACEA	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	Y
benzoyl peroxide	PANOXYL	TOPICAL	CLEANSER	Y
benzoyl peroxide	BENZEFOAM	TOPICAL	FOAM	Y
benzoyl peroxide	ACNE MEDICATION	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 10	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 2.5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZAC W 5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	PANOXYL AQ 2.5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	PANOXYL AQ 5	TOPICAL	GEL (GRAM)	Y
benzoyl peroxide	BPO	TOPICAL	TOWELETTE	Y
clindamycin phos/benzoyl perox	BENZACLIN	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	NEUAC	TOPICAL	GEL (GRAM)	Y
clindamycin phos/benzoyl perox	ACANYA	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	BENZACLIN	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL W/PUMP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	FOAM	Y
clindamycin phosphate	EVOCLIN	TOPICAL	FOAM	Y
clindamycin phosphate	CLEOCIN T	TOPICAL	GEL (GRAM)	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL (GRAM)	Y
clindamycin phosphate	CLEOCIN T	TOPICAL	LOTION	Y

clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	LOTION	Y
clindamycin phosphate	CLINDACIN ETZ	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDACIN P	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	MED. SWAB	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	SOLUTION	Y
clindamycin/tretinoin	CLINDAMYCIN PHOS-TRETINOIN	TOPICAL	GEL (GRAM)	Y
clindamycin/tretinoin	ZIANA	TOPICAL	GEL (GRAM)	Y
dapsone	ACZONE	TOPICAL	GEL (GRAM)	Y
dapsone	DAPSONE	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERYGEL	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	GEL (GRAM)	Y
erythromycin base in ethanol	ERY	TOPICAL	MED. SWAB	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	MED. SWAB	Y
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	SOLUTION	Y
isotretinoin	ABSORICA	ORAL	CAPSULE	Y
isotretinoin	AMNESTEEM	ORAL	CAPSULE	Y
isotretinoin	CLARAVIS	ORAL	CAPSULE	Y
isotretinoin	ISOTRETINOIN	ORAL	CAPSULE	Y
isotretinoin	MYORISAN	ORAL	CAPSULE	Y
isotretinoin	ZENATANE	ORAL	CAPSULE	Y
sulfacetamide sodium	KLARON	TOPICAL	SUSPENSION	Y
sulfacetamide sodium	SULFACETAMIDE SODIUM	TOPICAL	SUSPENSION	Y
tretinoin	AVITA	TOPICAL	CREAM (G)	Y
tretinoin	RETIN-A	TOPICAL	CREAM (G)	Y
tretinoin	TRETINOIN	TOPICAL	CREAM (G)	Y
tretinoin	ATRALIN	TOPICAL	GEL (GRAM)	Y
tretinoin	AVITA	TOPICAL	GEL (GRAM)	Y
tretinoin	RETIN-A	TOPICAL	GEL (GRAM)	Y
tretinoin	TRETINOIN	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	RETIN-A MICRO	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	TOPICAL	GEL (GRAM)	Y
tretinoin microspheres	RETIN-A MICRO PUMP	TOPICAL	GEL W/PUMP	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	TOPICAL	GEL W/PUMP	Y
adapalene	PLIXDA	TOPICAL	MED. SWAB	N
adapalene	ADAPALENE	TOPICAL	SOLUTION	N
adapalene/benzoyl peroxide	EPIDUO FORTE	TOPICAL	GEL W/PUMP	N
azelaic acid	AZELEX	TOPICAL	CREAM (G)	N
azelaic acid	FINEVIN	TOPICAL	CREAM (G)	N
azelaic acid	FINACEA	TOPICAL	FOAM	N
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	N

benzoyl peroxide	PANOXYL-4	TOPICAL	CLEANSER	N
clindamycin phos/benzoyl perox	ONEXTON	TOPICAL	GEL (GRAM)	N
clindamycin phos/benzoyl perox	ONEXTON	TOPICAL	GEL W/PUMP	N
clindamycin phos/skin clnsr 19	CLINDACIN ETZ	TOPICAL	KIT	N
clindamycin phos/skin clnsr 19	CLINDACIN PAC	TOPICAL	KIT	N
clindamycin phosphate	CLINDAGEL	TOPICAL	GEL DAILY	N
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL DAILY	N
clindamycin/benzoyl/emol cmb94	NEUAC	TOPICAL	CMB CR GEL	N
dapsone	ACZONE	TOPICAL	GEL W/PUMP	N
dapsone	DAPSONE	TOPICAL	GEL W/PUMP	N
erythromycin/benzoyl peroxide	AKTIPAK	TOPICAL	GEL (EA)	N
erythromycin/benzoyl peroxide	BENZAMYCIN	TOPICAL	GEL (GRAM)	N
erythromycin/benzoyl peroxide	ERYTHROMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	N
isotretinoin	ABSORICA	ORAL	CAPSULE	N
isotretinoin, micronized	ABSORICA LD	ORAL	CAPSULE	N
tazarotene	FABIOR	TOPICAL	FOAM	N
tazarotene	ARAZLO	TOPICAL	LOTION	N
tretinoin	TRETIN-X	TOPICAL	CREAM (G)	N
tretinoin	ALTRENO	TOPICAL	LOTION	N
tretinoin microspheres	RETIN-A MICRO PUMP	TOPICAL	GEL W/PUMP	N
tretinoin/emol 9/skin cleansr1	TRETIN-X	TOPICAL	COMBO. PKG	N
trifarotene	AKLIEF	TOPICAL	CREAM (G)	N
benzoyl peroxide	ACNE MEDICATION	TOPICAL	LOTION	
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	LOTION	

Appendix 2: Abstracts of Comparative Clinical Trials

n/a

Appendix 3: Medline Search Strategy

1	Adapalene/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	32
2	azelaic acid.mp.	759
3	Benzoyl Peroxide/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	633
4	Clindamycin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	3295
5	Dapsone/ae, th, to [Adverse Effects, Therapy, Toxicity]	849
6	Erythromycin/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	5145
7	Isotretinoin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	2133
8	Sulfacetamide/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	123
9	Tretinoin/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]	4923
10	Adapalene, Benzoyl Peroxide Drug Combination/ or Adapalene/	388
11	tazarotene.mp.	603
12	trifarotene.mp.	19
13	Contraceptives, Oral/ae, tu, th, to [Adverse Effects, Therapeutic Use, Therapy, Toxicity]	9731
14	Acne Vulgaris/	11742
15	Acne Conglobata/	20
16	acne fulminans.mp.	186
17	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	27658
18	14 or 15 or 16	11798
19	17 and 18	2486
20	limit 19 to (english language and (adaptive clinical trial 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 randomized controlled trial or "systematic review"))	659
21	limit 20 to yr="2019 -Current"	29
22	Clascoterone.mp.	13
23	CB-03-01.mp.	6
24	22 or 23	13
25	20 and 24	1

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

WINLEVI® (clascoterone) cream, for topical use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

WINLEVI® (clascoterone) cream is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening). Avoid contact with eyes, mouth, and mucous membranes. (2)
- Not for ophthalmic, oral or vaginal use. (2)

DOSAGE FORM AND STRENGTHS

Cream 1%. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Local Irritation: Pruritus, burning, skin redness or peeling may be experienced with WINLEVI cream. If these effects occur, discontinue or reduce the frequency of application of WINLEVI cream. (5.1)
- Hypothalamic-pituitary-adrenal (HPA) axis suppression may occur during or after treatment with clascoterone. (5.2)
- Attempt to withdraw use if HPA axis suppression develops. (5.2)
- Pediatric patients may be more susceptible to systemic toxicity. (5.2, 8.4)
- Hyperkalemia: Elevated potassium levels were observed in some subjects during the clinical trials. (12.2)

ADVERSE REACTIONS

Most common adverse reactions occurring in 7 to 12% of patients are erythema/reddening, pruritus and scaling/dryness. Additionally, edema, stinging, and burning occurred in >3% of patients and were reported in a similar percentage of subjects treated with vehicle. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cassiopea at 1-855-WINLEVI or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

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

Revised: 8/2020

Appendix 5: Key Inclusion Criteria

Population	Adults and children with acne conglablata, acne fulminans, or severe acne vulgaris
Intervention	Clascoterone topical therapy, other acne therapies (see **appendix 3**), spironolactone, oral contraceptives
Comparator	Placebo or active treatment
Outcomes	Inflammatory and noninflammatory lesion reduction, adverse reactions
Timing	Not applicable
Setting	Outpatient therapy

Acne Medications

Goal(s):
- Ensure that medications for acne are used appropriately for OHP-funded conditions.

Length of Authorization:
- Up to 12 months

Requires PA:
- All drugs in the Acne medications class

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 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. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and process appropriate PA.	**No:** Approve for 12 months.

P&T/DUR Review: 02/21 (SF); 06/2020 (SF); 11/18 (JP)
Implementation: 7/1/20; 1/1/1

Author: Fletcher Date: February 2021

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

OHSU Drug Effectiveness Review Project Summary Report – Palforzia and Viaskin Peanut for Peanut Allergy: Clinical Evidence

Date of Review: December 2020
Generic Name: Peanut (arachis hypogaea) allergen powder-dnfp
PDL Class: none

End Date of Literature Search: 03/01/2020
Brand Name (Manufacturer): Palforzia (Aimmune Therapeutics)
Dossier Received: yes

Research Questions:

1. What is the effectiveness of Palforzia (powder capsules/packet) and Viaskin Peanut (patch) for peanut allergy?
2. What are the harms of powder capsules/packet and peanut patch for peanut allergy?

Conclusions:

- The evidence included in the review is based on findings from the 2020 Drug Effectiveness Review Project (DERP) report on powder capsules/packet for Peanut Allergy.
- There were 5 studies included in this review. All used a baseline, double-blind, placebo-controlled food challenge (DBPCFC) test plus either laboratory or skin-patch testing to confirm peanut allergy. There was variation across studies regarding threshold of peanut protein consumption needed to elicit symptoms, and therefore ranges of allergy severity included.
- Efficacy was defined as ability to consume peanut protein on exit DBPCFC test without symptoms. Quantity of peanut protein varied across studies for this endpoint from 300 mg to 5,000 mg or as a set increase from baseline, such as 10 times more at exit than baseline eliciting dose.
- Low quality studies showed that at 12 months powder capsules/packet (67% to 79%; number needed to treat [NNT] 2) were significantly able to increase pass rate for a DBPCFC test when compared to placebo (4% to 19%).
- Very low quality evidence showed that recipients of powder capsules/packet were more likely to require use of epinephrine outside of a food challenge, when compared to patients taking placebo (14% vs 6.5%; Absolute risk reduction [ARR] 7.5%, number needed to harm [NNH] 13). Outcome reported in 1 of 2 studies.
- Epinephrine use during exit DBPCFC was less common in powder capsules/packet patients (9% and 10%) than those taking placebo (42% and 53%) (ARR 33% and 43%, NNT 3). Outcome not graded.
- No serious adverse events were observed in 1 study. In a second study, 4.3% of powder capsules/packet and 0.8% of placebo patients experienced severe AE outside of the DBPCFC.
- Low quality evidence showed that powder capsules/packet patients were more likely to discontinue due to adverse events than placebo patients in 2 RCT (21% vs. 0% and 11.6% vs. 2.4%). Mild gastrointestinal side effects were the most common cause, though moderate and severe reactions such as anaphylaxis and systemic allergic reactions were also reported.
- There are no data related to quality of life, emergency department use, or hospital admission.
- There are no data to determine duration of effect, if ongoing medication use or low-dose peanut consumption can sustain desensitization, and the comparative effectiveness of the two products.

Author: Sara Fletcher, PharmD, MPH, BCPS

Recommendations:

- Create “Peanut Desensitization” PDL class within Immunology.
- Designate Palforzia (powder capsules/packet) as non-preferred based on clinical information.
- Implement Prior Authorization criteria to ensure appropriate use of Palforzia (powder capsules/packet) for funded conditions.

Background:

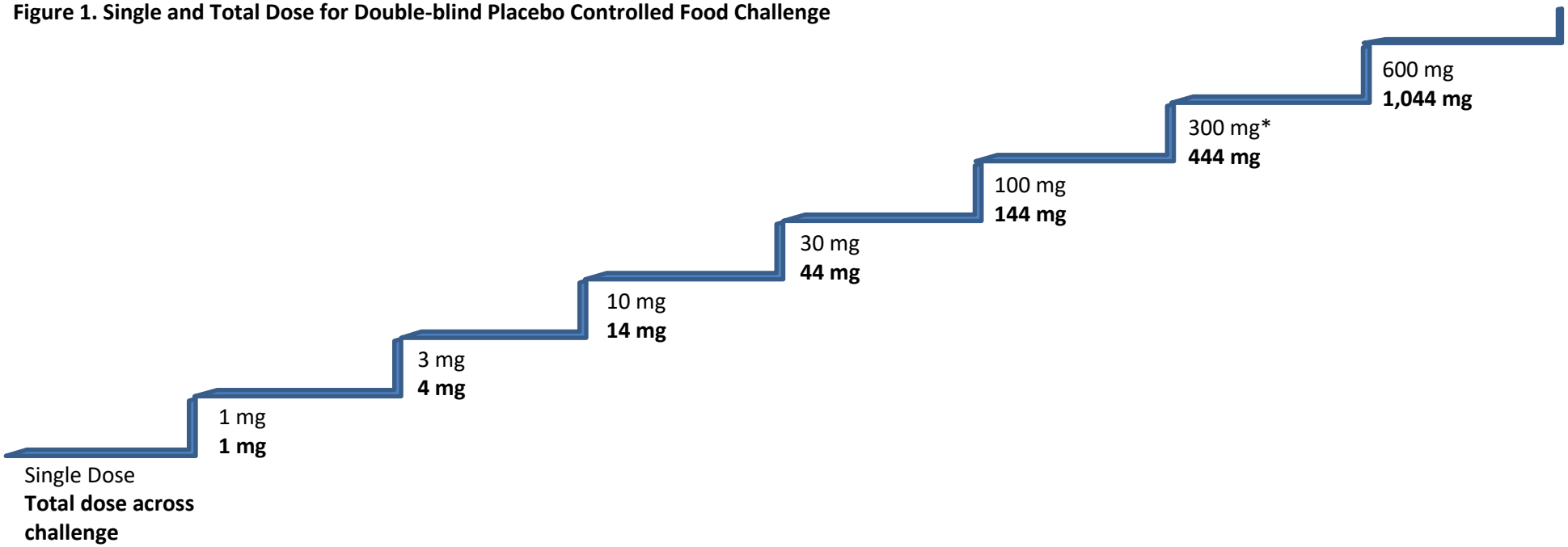
The purpose of this DERP report is to summarize the efficacy and harms from powder capsules/packet and peanut patch, which are potential immunotherapy treatment options for peanut allergy**.**

Peanut allergy affects approximately 2% of children and adults, and generally persists over the lifetime. Symptoms range from mild, such as tongue tingling, to severe, which can result in circulatory collapse, respiratory distress, and death. Peanuts are ubiquitous in the food supply, and while a single peanut is generally 250 to 300 mg, some people can exhibit objective allergic reactions with ingestion of only 5 to 10 mg of peanut protein. Patients generally focus on dietary avoidance combined with symptom management using antihistamines and epinephrine after accidental ingestion/exposure.

Serum immunoglobulin E (IgE) levels and skin-prick testing are common tools to identify sensitivity to a food substance. Thresholds may vary and in clinical trials are often an IgE level of ≥ 0.35 kU_A/L or ≥ 0.7 kU_A/L or a skin wheal ≥ 3 mm, ≥ 6 mm, or ≥ 8 mm. However, sensitization does not always translate into allergy. Many patients will tolerate a food challenge despite sensitization. Peanut allergy diagnosis is therefore clinical and necessitates known consumption of the offending agent. A DBPCFC is the gold standard to assess efficacy of a study drug for peanut desensitization, however there are administration challenges and limitations. These are conducted over 2 days in which both patient and assessor are blinded; one day containing a placebo and the other the allergen. Protocols and assessment criteria (e.g., subjective or objective symptoms) vary, and there is no “standard threshold” of tolerated peanut consumption for successful desensitization. Desensitization rarely results in the ability to consume any amount of peanut without symptoms. DBPCFC should be done at baseline and, after treatment with the study product, using more of the allergen. **Figure 1** illustrates a stepwise increase in allergen consumption in DBPCFC often seen in peanut immunotherapy research studies.

The Oregon Health Plan prioritized list includes funding for peanut allergy treatment in guideline note 203. Pharmaceutical treatment with medications to reduce severity are included on line 123 when specified criteria are met. Peanut allergy must be diagnosed clinically based on history of serious reaction or anaphylaxis, with skin or serologic testing, and with a DBPCFC. Any treatment must be by, or in consultation with, an allergist or immunologist.

Figure 1. Single and Total Dose for Double-blind Placebo Controlled Food Challenge



* Equivalent to approximately one peanut.
Note: Consuming the 100 mg single dose without symptoms, but then developing symptoms at the 300 mg is categorized as an eliciting dose of > 100 mg or > 144 mg total dose.

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

Methods:
The June 2020 drug class report on powder capsules/packet and peanut patch for Peanut Allergy by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. The literature search was conducted through March 2020.

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

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

Summary Findings:

There was heterogeneity across studies particularly for inclusion criteria, definition of peanut allergy, exclusion criteria, and definition of successful desensitization. Study descriptions are included below with results by graded outcome described in **Table 1**.

Efficacy:

Palforzia (powder capsules/packet):

Palforzia (powder capsules/packet) was approved for peanut allergy immunotherapy for patients ages 4 to 17 on January 31st, 2020.

ARC001
A phase 2, placebo-controlled randomized-controlled trial (RCT) of 56 patients based in the US was conducted to compare powder capsules/packet to placebo. (Moderate RoB) Patients were 4 to 26 years of age with a clinical history of peanut allergy with an eliciting dose (ED) of ≤ 100 mg *and* sensitivity demonstrated by IgE ≥ 0.35 kU_A/L or skin prick wheal ≥ 3 mm. Patients were excluded for a history of frequent or repeated severe or life-threatening anaphylaxis, eosinophilic gastrointestinal disease, or severe/uncontrolled asthma. Graduated doses of powder capsules/packet were mixed into age-appropriate foods and given to participants, with a goal of 300 mg/day by week 34. An exit DBPCFC was done after 2 continuous weeks of powder capsules/packet 300 mg/day, this resulted in 79% powder capsules/packet versus 19% placebo patients tolerating an ED of ≥300 mg at 34 weeks [ARR 60%, NNT 2; relative risk (RR) 4.12, 95% CI 1.8 to 9.2, P<0.001].

PALISADE
A phase 3, placebo-controlled RCT of 499 patients across North America and Europe was conducted to compare powder capsules/packet to placebo. (High RoB) Patients were aged 4 to 55 years, though the prespecified population was 4-17 years and the 56 patients aged 18 to 55 years were enrolled for a separate analysis. Results below reflect data from the 4-17 year old participants only. Patients required the same peanut allergy and sensitization thresholds as in ARC001 and had similar exclusion criteria. Graduated doses of powder capsules/packet up to a goal of 300 mg were given, with a maintenance dose continued for 24 weeks. An exit DBPCFC was conducted after 52 weeks and 67.2% powder capsules/packet and 4% of placebo patients were able to tolerate an ED ≥ 600 mg [NNT 2; risk difference (RD) 63.2%, 95% CI 53.0 to 73.3%, P<0.001; RR 16.6, 95% CI 7.0 to 39.4, P<0.001].

RoB of these studies was downgraded due to financial conflicts of interest among authors, differential lost to follow-up, manufacturer involvement, limited generalizability, and composite outcomes.

Viaskin Peanut (patch):

Viaskin Peanut (patch) is not currently a FDA approved product and was denied approval in August 2020 due to patch adhesion concerns. Modifications and additional human studies were requested.

PEPITES
A phase 3, placebo-controlled RCT of 356 patients in North American, Western Europe, and Australia was conducted to compare peanut patch (250 µg) to placebo patches. (Moderate RoB) Patients were 4 to 11 years of age with of ED of ≤ 300 mg and IgE ≥ 0.7 kU_A/L or skin prick wheal ≥ 6 mm. A low ED of ≤ 10 mg was present for 11.5% of patients. Individuals with uncontrolled asthma or a history of severe anaphylaxis were excluded. The patches were applied for an increasing proportion of the day over 2 weeks to a goal of 24 hours/day. At week 52, an ED ≥ 300 mg in the low ED group or ≥ 1000 mg in the high ED group was tolerated in 35.3% peanut patch and 13.6% placebo patients (ARR 21.7%, NNT 5; RD 21.7%, 95% CI 12.4 to 29.8%, P=0.001; RR 2.6, 95% CI 1.59 to 4.23, P=0.0001). While statistically significant, this outcome did not meet the prespecified relevance criterion of ≥ 15% RD for the lower bound of the CI as determined by the study protocol.

COFAR
A phase 2, placebo-controlled RCT of 74 patients was conducted to compare 100 µg, 250 µg, and placebo patches. Included were 4 to 25 year-olds with a physician diagnosis *or* a combination of history of peanut allergy and IgE ≥ 0.35 kU_A/L and an ED of ≤ 600 mg on oral food challenge. Patients were excluded for a history of severe anaphylaxis or chronic diseases. At week 52, an ED ≥ 5044 mg (total, see **Figure 1**) *or* 10-fold increase from baseline tolerated dose was met in 48% of 250 µg peanut patch vs. 45.8% of 100 µg peanut patch vs. 12% of placebo patients (statistical variance not reported).

VIPES
A phase 2b, placebo-controlled RCT of 221 patients in North American and Europe was conducted to compare 50 µg, 100 µg, 250 µg, and placebo patches. Patients 6 to 55 years of age were included if they had a clinical history of peanut allergy with an ED of ≤ 300 mg *and* IgE ≥ 0.7 kU_A/L or skin prick wheal of ≥ 8 mm. Individuals with chronic diseases, unstable asthma, and history of severe anaphylaxis were excluded. The patches were applied for an increasing proportion of the day over 2 weeks to a goal of 24 hours/day. At week 52, patients were able to tolerate an ED ≥ 1000mg or 10-fold increase from baseline ED in the following percentages (ARR and RR vs. placebo for all): 250 µg peanut patch 50% (ARR 25%, NNT 4; RR 2.0, 95% CI 1.2 to 3.4), 100 µg peanut patch 41.1% (ARR 16%, NNT 7; RR 1.6, 95% CI 0.9 to 2.8), 50 µg peanut patch 45.3% (ARR 20%, NNT 5; RR 1.8, 95% CI 1.0 to 3.1), and placebo 25%.

RoB of these studies was downgraded due to financial conflicts of interest among authors, composite outcomes, limited generalizability, and manufacturer involvement.

Two additional studies for peanut patch were completed more than 5 years ago and do not have published results available, indicating possible publication bias. There are at least 15 additional studies for both products in process or recently completed, some with patient age ranges below the FDA powder capsules/packet approval of 4 to 17 years. Open-label extension studies may soon provide information related to longer-term outcomes.

Safety:

Palforzia (powder capsules/packet):
Adverse events (AE) in the two RCT were common and occurred with greater frequency in powder capsules/packet patients than placebo (96.6% and 98.7% compared to 84.6% and 95.2%). Most common AE were abdominal pain, vomiting, oral itching, hives, sneezing, cough, and shortness of breath. Use of epinephrine during food challenge was more common for placebo patients (42% and 53%) compared to powder capsules/packet treated patients (9% and 10%). Epinephrine use outside of the food challenge was only reported in PALISADE; 14% of powder capsules/packet and 6.5% of placebo patients required epinephrine use (ARR 7.5%; NNH 13; RR 2.16, 95% CI 1.05 to 4.43, P=0.003). Adherence information was collected but not fully reported. Hospitalization and emergency department use were not reported.

No serious adverse events were observed in ARC001. In PALISADE, 4.3% of powder capsules/packet and 0.8% of placebo patients experienced severe AE outside of the DBPCFC. These included systemic allergic reactions, asthma exacerbations, and anaphylaxis. Treatment emergent AE (TEAE) were more common in powder capsules/packet treated patient than placebo patients across all age groups (86.1% to 69.7% in 4 to 11 years, 89.6% to 68.6% in 12 to 17 years, and 87.8% to 78.6% in 18 to 55 years). Powder capsules/packet patients were more likely to discontinue due to adverse events than placebo in both RCT (21% vs. 0% and 11.6% vs. 2.4%). Mild gastrointestinal side effects were the most common cause, though moderate and severe reactions such as anaphylaxis and systemic allergic reactions were also reported.

Viaskin Peanut (patch):
Overall AE reported in 2 RCT and were more common in peanut patch patients than those receiving placebo (95.4% vs. 89% and 79.8% vs. 14.4%). These include primarily patch site reactions such as itching, redness, and swelling, but full analysis was not reported. Serious adverse events were similar in one study and more common in peanut patch patients than placebo in a second RCT. Severe TEAE were greater in peanut patch patients (3.8% to 17.9%; increasing with higher doses) versus placebo (7.1%). Discontinuations were similar for peanut patch (1.8% to 12.5%) and placebo recipients (0 to 8%) and were due to patch site irritation and dermatitis.

No studies included epinephrine use as an outcome, however the PEPITES RCT reported 4.2% of peanut patch patients and 5.1% of placebo patients had a serious TEAE outside of the DBPCFC, and all received epinephrine. Hospitalization was again not reported as an outcome, though 3 peanut patch recipients who accidently consumed peanut presented to the emergency department and received epinephrine.

Table 1: Summary of Results of Palforzia (powder capsules/packet) and Viaskin Peanut (patch) Randomized Controlled Trials

Outcome	Description	GRADE
Palforzia (powder capsules/packet)		
Change in severity of allergic response 2 studies: N = 555	Recipients of powder capsules/packet more likely to tolerate peanut protein at end of study compared to placebo. At 34 weeks: RR, 4.12; 95% CI, 1.8 to 9.2 At 52 weeks: RR, 16.6; 95% CI, 7.0 to 39.4	Low
Use of epinephrine 1 study: N = 499	Recipients of powder capsules/packet were more likely to use epinephrine outside of DBPCFC than placebo recipients Estimates of epinephrine 14% for powder capsules/packet vs. 6.5% for placebo	Very low
Hospitalization or emergency department use	No studies reported on this outcome	No rating
Quality of life	No studies reported on this outcome	No rating
Overall adverse events 2 studies: N = 555	While common across all participants, overall adverse events were more common for powder capsules/packet recipients Estimates range from 96.6% to 98.7% for powder capsules/packet compared to 84.6% to 95.2% for placebo at 34 to 52 weeks.	Very low
Serious adverse events 2 studies: N = 555	Serious adverse events were more common for powder capsules/packet recipients, however severe reactions (death, life threatening) were not observed. Estimates of serious adverse events range from 4.3% to 5.6% for powder capsules/packet compared to 0.8% to 1.6% for placebo recipients at 34 to 52 weeks. Neither study observed severe events (life-threatening or death).	Very low
Discontinuation of therapy due to adverse events 2 studies: N = 555	Powder capsules/packet recipients were more likely to discontinue due to adverse events (commonly gastrointestinal symptoms) Estimates of discontinuation ranged from 11.6% to 20.6% for powder capsules/packet compared to 0 to 2.4% for placebo at 34 to 52 weeks.	Low
Viaskin Peanut (patch)		
Change in severity of allergic response 3 studies: N = 651	Peanut patch recipients were more likely to tolerate peanut protein at 12 months compared to placebo in 3 studies using 250 µg dose. In 1 study, the lower bound of the confidence interval for the risk difference did not meet a prespecified clinically meaningful difference threshold. RD, 21.7; 95% CI, 12.4 to 29.8; *P* = .001 RR, 2.6; 95% CI, 1.59 to 4.23; *P* < .001 Reported RR 2.0 (95% CI, 1.2-3.4; no P value reported)	Low
Use of epinephrine	Narrative description in 1 small study. Authors state no epinephrine was used by any individual to treat dosing symptoms.	No rating
Hospitalization or emergency department use	No studies reported on this outcome	No rating

Quality of life	No studies reported on this outcome	No rating
Overall adverse events 2 studies: N = 430	Adverse events while common across all participants, appear more common for peanut patch recipients Estimates of adverse events ranged from 79.8% to 95.4% for peanut patch recipients compared to 14.4% to 89% for placebo at 12 months	Very low
Serious adverse events 2 studies: N =577	Serious adverse events appear similar for both peanut patch and placebo recipients in 1 study but greater for peanut patch recipients in another.	Very low
Discontinuation of therapy due to adverse events 3 studies: N = 651	Discontinuation of therapy was no different for peanut patch recipients compared to placebo Estimates range from 1.7% to 12.5% for peanut patch compared to 0 to 8% for placebo.	Very low

References:

1. Drug Effectiveness and Review Project (DERP). Palforzia and Viaskin Peanut for Peanut Allergy: Clinical Evidence. Center for Evidence-based Policy, Oregon Health & Science University; June 2020.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PALFORZIA safely and effectively. See Full Prescribing Information for PALFORZIA.

PALFORZIA [Peanut (*Arachis hypogaea*) Allergen Powder-dnfp]
Powder for oral administration
Initial U.S. Approval: 2020

WARNING: ANAPHYLAXIS
See Full Prescribing Information for complete boxed warning.

- **PALFORZIA can cause anaphylaxis, which may be life-threatening and can occur at any time during PALFORZIA therapy (5.1).**
- **Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use (5.1).**
- **Do not administer PALFORZIA to patients with uncontrolled asthma (4).**
- **Dose modifications may be necessary following an anaphylactic reaction (2.5).**
- **Observe patients during and after administration of the Initial Dose Escalation and the first dose of each Up-Dosing level, for at least 60 minutes (2.4).**
- **PALFORZIA is available only through a restricted program called the PALFORZIA REMS (5.2).**

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

PALFORZIA is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. PALFORZIA is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up-Dosing and Maintenance may be continued in patients 4 years of age and older (2.4).

PALFORZIA is to be used in conjunction with a peanut-avoidant diet.

Limitation of Use: Not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

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

For oral administration only (2)
- Do not swallow capsule(s).
- Do not inhale powder.
- Open capsule(s) or sachet and empty the entire dose of PALFORZIA powder onto refrigerated or room temperature semisolid food.
- Mix well.
- Consume the entire volume.

Initial Dose Escalation

Total Dose	Dose Configuration
0.5 mg	One 0.5 mg capsule
1 mg	One 1 mg capsule
1.5 mg	One 0.5 mg capsule; One 1 mg capsule
3 mg	Three 1 mg capsules
6 mg	Six 1 mg capsules

Up-Dosing

Total Daily Dose	Daily Dose Configuration
3 mg	Three 1 mg capsules
6 mg	Six 1 mg capsules
12 mg	Two 1 mg capsules; One 10 mg capsule
20 mg	One 20 mg capsule
40 mg	Two 20 mg capsules
80 mg	Four 20 mg capsules
120 mg	One 20 mg capsule; One 100 mg capsule
160 mg	Three 20 mg capsules; One 100 mg capsule
200 mg	Two 100 mg capsules
240 mg	Two 20 mg capsules; Two 100 mg capsules
300 mg	One 300 mg sachet

Maintenance

Total Daily Dose	Daily Dose Configuration
300 mg	One 300 mg sachet

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

Powder for oral administration supplied in 0.5 mg 1 mg, 10 mg, 20 mg and 100 mg Capsules or 300 mg Sachets.

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

- Uncontrolled asthma (5.3).
- History of eosinophilic esophagitis or other eosinophilic gastrointestinal disease (5.4 and 5.5).

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

- Anaphylaxis: PALFORZIA can cause anaphylaxis. Educate patients to recognize the signs and symptoms of anaphylaxis. Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use (5.1).
- Asthma: Ensure patients with asthma have their asthma under control prior to initiation of PALFORZIA. PALFORZIA should be temporarily withheld if the patient is experiencing an acute asthma exacerbation. PALFORZIA has not been studied in patients with severe asthma (5.3).
- Eosinophilic esophagitis: PALFORZIA is associated with eosinophilic esophagitis. Monitor patients for signs and symptoms and discontinue PALFORZIA if eosinophilic esophagitis is suspected (5.4).
- Gastrointestinal reactions: If patients develop chronic or recurrent local gastrointestinal allergic symptoms, consider dose modification or discontinuation of treatment (5.5).

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

The most common adverse reactions reported in subjects treated with PALFORZIA (incidence ≥ 5% and at least 5 percentage points greater than that reported in subjects treated with placebo) are abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylactic reaction, and ear pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics at toll-free phone 1-833-246-2566 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2020

December 2020

Peanut (arachis hypogaea) allergen powder-dnfp (Palforzia)

Goal(s):
- To ensure appropriate use of desensitization products in patients with peanut allergies

Length of Authorization:
- Initial: 12 months
- Renewal: Up to 12 months

Requires PA:
- Peanut (arachis hypogaea) allergen powder-dnfp (Palforzia) (both pharmacy and physician administered claims)

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP? Line 123, Guideline note 203	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request by, or in consultation with, an allergist or immunologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for continuation of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the request for an FDA-approved indication and age?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have a history of serious peanut allergy or anaphylaxis?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
7. Is there baseline documentation of number of epinephrine administrations and hospital/emergency department visits in past 12 months.	**Yes:** Go to #8 Epi administrations:_____ Hospital/ED visits:_____	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a history of severe peanut reaction that included circulatory shock or need for mechanical ventilation?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have a peanut-specific positive IgE of ≥ 0.35 kU_a/L OR a skin prick test wheal of ≥ 3 mm?	**Yes**: Go to #10	**No:** Pass to RPh. Deny; not funded by the OHP
10. Does the patient have a peanut allergy confirmed with a double-blind, placebo-controlled food challenge?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP
11. Does the patient have uncontrolled asthma, history of eosinophilic esophagitis, or other eosinophilic gastrointestinal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Are the healthcare setting and the prescriber certified in the Palforzia REMS program AND will the patient be enrolled in the REMS program upon PA approval?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for the full 300 mg daily maintenance dose of peanut allergen powder?	**Yes**: Go to #3	**No:** Go to #2

Renewal Criteria		
2. Is the patient new to OHA FFS and has the patient not yet completed the initial dose titration prior to FFS enrollment?	**Yes:** Approve for 12 months; Document baseline epinephrine use and hospital/emergency department visits	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient had a reduced number of allergic attacks since beginning peanut allergen powder as evidenced by either: • Decreased number of needed epinephrine administrations OR • Decreased number of hospital/emergency department visits	**Yes**: Approval for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/21 (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 Literature Scan: Tobacco Smoking Cessation

Date of Review: February 2021

Date of Last Review: September 2019
Literature Search: July 2019 – December 2020

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

Purpose of Review:
- Provide new comparative effectiveness and safety evidence for smoking cessation therapeutic agents published since the last literature scan.
- Update Oregon Health Plan Fee-for-Service (OHP-FFS) prior authorization (PA) criteria to align with Health Evidence Review Commission (HERC) guidance.

Conclusions:
- Four systematic reviews and 2 clinical practice guidelines were identified which evaluated smoking cessation interventions in patients with tobacco dependence.
- The identified literature found no new current comparative evidence to demonstrate a difference in clinical efficacy or safety among FDA-approved pharmacological agents.
- No comparative evidence was found to favor the use of one specific smoking cessation intervention type over another to promote long term abstinence in any subpopulation.
- One American Thoracic Society (ATS) guideline recommended varenicline therapy over nicotine patch for initial treatment of adults with tobacco dependence as well as for adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder (strong recommendation, moderate certainty in the estimated effects).
- Prior Authorization Criteria for nicotine replacement therapy and bupropion HCl as smoking cessation treatments is supported by current federal and state policy but varenicline therapy requires an update to allow for two 12-week treatment regimens within 1 year for patients 17 years of age and older.

Recommendations:
- Recommend no changes to the current PDL based on new comparative evidence.
- Update PA criteria to allow varenicline therapy for two 12-week treatment regimens within 1 year for patients 17 years of age and older.
- Evaluate comparative costs in the executive session.

Author: David Engen, PharmD

Summary of Prior Reviews and Current Policy

High quality evidence identified from previous reviews demonstrated that combined pharmacotherapy and behavioral treatment were more effective than usual care, brief advice, or less intensive support in the treatment of tobacco dependence. The Health Evidence Review Commission (HERC) outlined tobacco cessation coverage benefits and standards for the OHP population which may currently be found on Line 5 of the Prioritized List. In January 2014 the Affordable Care Act (ACA) required health insurance plans to cover without cost sharing all preventive services that had received "A" or "B" ratings from the US Preventive Services Task Force.[1] In May 2014, the Department of Health and Human Services clarified what constitutes a comprehensive tobacco cessation benefit under the ACA.[1] In Oregon, the HERC requirements for tobacco cessation coverage under Medicaid are aligned with the ACA requirements. [1] According to these requirements, a group health plan or health insurance issuer must cover the following:

1. Screening for tobacco use
2. For those who use tobacco products, at least two tobacco cessation attempts per year, recognizing not everyone quits on their first try. For this purpose, covering a cessation attempt includes coverage for:
    - Four tobacco counseling sessions of at least 10 minutes each (including telephone, group and/or individual counseling)
    - All medications approved by the FDA as safe and effective for smoking cessation (including both prescription and over-the-counter medications) for a 90-day treatment regimen when prescribed by a health care provider
    - Plans should not require prior authorization to access these benefits
    - Cessation benefits shall be provided at no cost to the patient. No copays, coinsurance or deductibles should be charged

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all FDA-approved smoking cessation agents are covered including varenicline, bupropion and all forms of nicotine replacement therapy. Current prior authorization (PA) policy requires a PA for non-preferred products; use of NRT beyond 6 months in the absence of behavioral counseling; and varenicline treatment for more than 12 weeks or for patients less than 17 years of age. In April through June of 2020, approximately 86% of the PA requests were initially approved, 6% had a paid claim within 30 days for either the requested agent or a similar agent, and only 8% did not have a paid claim after a denial mostly due lost eligibility or other insurance enrollment.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. 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 the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

A 2020 Cochrane Systematic Review evaluated the safety and efficacy of pharmacological interventions for smoking cessation during pregnancy.[2] The primary outcome was biochemically validated smoking cessation at the latest point in pregnancy ($\geq$20 weeks gestation). [2] Eleven randomized controlled trials (N=2412)

with pregnant women were included in the review.[2] Nine of the trials investigated nicotine replacement therapy (NRT) and 2 of the trials studied bupropion, both of which were compared to either placebo or behavioral support.[2] Nine studies revealed low quality evidence that NRT increased the likelihood of smoking abstinence in late pregnancy compared to placebo or behavioral support alone (RR 1.37, 95% CI 1.08 to 1.74; I^2 = 34%; N=2336).[2] The benefit was greater with NRT compared to behavioral therapy alone (Risk Ratio, (RR) 8.55, 95% CI 2.05 to 35.71; I^2 = 0%, 3 studies, N=273) while there was unclear benefit in NRT compared to placebo (RR 1.21, 95% CI 0.95 to 1.55; I^2 = 0%, 6 studies, N=2063).[2] There was no apparent statistically significant difference in effectiveness between fast acting NRT and patches (Test for subgroup differences: Chi^2=3.13, df=1 (P=0.08), I^2=68.06%).[2] For safety, there was no evidence of differences between NRT and control groups in rates of caesarian section, birthweight, miscarriage, stillbirth, premature birth, neonatal intensive care admissions, congenital abnormalities, or neonatal death.[2] There was low-certainty evidence of no difference in smoking abstinence rates in later pregnancy for women treated with bupropion compared to placebo (RR 0.74, 95% CI 0.21 to 2.64; I^2 = 0%, 2 studies, N=76) as well as no reported differences in safety outcomes.[2]

A systematic review with meta-analysis was conducted to evaluate the safety and efficacy of pharmacological interventions to achieve smoking abstinence in adults with schizophrenia/schizoaffective disorder and/or bipolar disorders.[3] Most of the 28 RCTs identified (n=1947) measured biochemically validated abstinence rates at 3 and 6 months while a few assessed sustained abstinence from smoking at 52 weeks.[3] A 5-study meta-analysis (n=214) of schizophrenia patients treated with bupropion alone or in combination with NRT reported a statistically significant smoking cessation benefit at 6 months compared to placebo (Risk Ratio (RR) 3.04 (95% CI, 1.14 to 8.09, p=0.03, I^2=0%).[3] However, pooled results of the 3 studies with bupropion monotherapy compared to placebo showed no effect at 6 months.[3] Although pooled analysis of 2 studies (n=188) with varenicline reported a statistically significant difference smoking abstinence rates at 6 months compared with placebo (RR 3.69, 95% CI 1.08 to 12.60, p=0.04, I^2=0%), no effect was observed in patients with bipolar disorder or schizophrenia.[3] Neither bupropion or NRT was found to affect positive and negative symptoms, anxiety, or depressive symptoms, while analysis of varenicline studies showed a higher incidence of nausea and vomiting (RR 1.66 (1.23 to 2.24, p=0.0009).[3] Evidence for the bupropion and varenicline studies was considered very low quality due to the overall poor methodology of included studies, placebo comparisons, limited population size, and short study durations.[3] Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies were uncertain.[3]

A meta-analysis was conducted to evaluate the efficacy and safety of varenicline combined with bupropion to achieve abstinence in nicotine-dependent adult smokers.[4] Four RCTs (n=1230) compared the combination of varenicline plus bupropion to varenicline plus placebo.[4] Abstinence rates were assessed and biochemically confirmed at the conclusion of treatment, at 6 months, and 12 months follow-up.[4] All 4 trials were double blinded.[4] Although the overall quality of the studies was considered high, only one trial described the methods of randomization clearly and two studies had unclear allocation concealment.[4] Combination therapy with varenicline and bupropion were reported to show statistically significant rates of abstinence at the end of treatment compared to varenicline alone (RR 1.153, 95% CI 1.019 to 1.305, P=0.024; I^2=42.2%, P=0.158).[4] Abstinence rates at the 6 month follow-up (3 studies, n=1056) showed a benefit for combination therapy compared to varenicline alone (RR 1.23, 95% CI 1.02 to 1.50, P=0.033; I^2=27.8%, P=0.250) but no benefit was observed at the 12 month follow-up assessment (2 studies, n=835) for varenicline plus bupropion combination therapy.[4]

A Cochrane systematic review of 63 studies (N = 41,509) reviewed efficacy and safety of various forms, delivery systems, doses, and durations of NRT to achieve long-term abstinence.[5] Studies were at least 6 months duration and enrolled adult patients who typically smoked $\geq$15 cigarettes per day.[5] Those studies with placebo comparators or a relatively short outcome follow-up (i.e. <6 months) were excluded.[5] Based on data from 14 studies (n=11,356), there was high-certainty evidence of a higher rate of abstinence at 6 months with combination NRT (fast-acting formulation plus patch) compared to monotherapy (Risk Ratio (RR) 1.25, 95% CI 1.15 to 1.36; I^2=4%).[5] There was high-certainty evidence from 8 studies (n=3319) to indicate similar long-term quit rates for fast-acting NRT compared to nicotine patch (RR 0.90, 95%CI 0.77 to 1.05; I^2=0%).[5] One study (n=922) demonstrated significantly more withdrawals due to treatment for patients on nicotine nasal spray therapy compared to patch (RR 3.47, 95% CI 1.15 to 10.46), however, the findings were based on very low certainty evidence.[5]

Multiple systematic reviews, primarily Cochrane reviews, have been published to assess evidence for other smoking cessation strategies either used alone or in combination with pharmacotherapy to treat tobacco dependence or prevent relapse.[6,7] Alternative smoking cessation strategies included reduction, instruction, behavioral support, and/or electronic-cigarettes compared to no treatment/advice or abrupt quit interventions.[6] Evidence from these reviews was generally of insufficient to very low quality for clinical outcomes of interest upon comparison to placebo or other therapies.[6,7] Quality of evidence was often limited by high or unclear risk of bias, limited population size, or small effect sizes.[6,7] Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies are uncertain.[6,7]

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

New Guidelines:
The American Thoracic Society (ATS) released guidelines for initiation of pharmacologic treatment in tobacco-dependent adults.[8] The guideline was intended to be an extension of the US Public Health Service (USPHS) smoking cessation guidelines which focused on the efficacy of various interventions.[8] The ATS guideline goal was to provide more personalized, patient-centered recommendations for clinical questions of effectiveness in special populations and scenarios. Recommendations were based on the established Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria in terms of recommendation strength and certainty of estimated effects.[8] The strength of recommendations considered the benefits and harms of therapy, patient values and preferences, resource issues, practicability, and impartiality of different recommendations which were rated on a continuum and referred to as strong or weak.[8] The certainty of recommendations was graded as very low, low, moderate, or high quality based on risk of bias (including likelihood of publication bias), dose-effect, precision, consistency, and potential confounding.[8]

The guideline panel made 7 recommendations:
Strong Recommendations

- Use varenicline over a nicotine patch for initial treatment of adults with tobacco dependence (strong recommendation, moderate certainty in the estimated effects)[8]
- Use varenicline over bupropion for initial treatment of adults with tobacco dependence (strong recommendation, moderate certainty in the estimated effects)[8]
- Begin treatment with varenicline rather than wait until patients are ready to quit tobacco use in tobacco-dependent adults who are not ready to quit (strong recommendation, moderate certainty in the estimated effects)[8]
- Use varenicline over a nicotine patch for tobacco-dependent adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom tobacco cessation treatment is being initiated (strong recommendation, moderate certainty in the estimated effects)[8]
- Use extended-duration of therapy (>12 weeks) over standard duration (6–12 weeks) of therapy for tobacco-dependent adults for whom treatment is being initiated with a controller (strong recommendation, moderate certainty in the estimated effects)[8]

Conditional Recommendations

- Use varenicline plus a nicotine patch over varenicline alone for initial treatment of adults with tobacco dependence (conditional recommendation, low certainty in the estimated effects)[8]

- Use varenicline over electronic cigarettes for initial treatment of adults with tobacco dependence (conditional recommendation, very low certainty in the estimated effects) [8]

The ATS recommendations for tobacco dependence treatment of adults with comorbid psychiatric conditions did not compare varenicline with bupropion or other tobacco cessation agents.[8] Many of the ATS guideline's lead authors received research funding and/or have served on advisory committees for the manufacturer. [8]

Additional Guidelines for Clinical Context:
The United States Preventative Services Task Force (USPSTF) released a recommendation statement for primary care interventions for prevention and cessation of tobacco use in children and adolescents.[9] The recommendation was based on findings from an updated systematic review (n=44521) from primary care-relevant studies, randomized clinical trials, and nonrandomized controlled intervention studies that compared behavioral or pharmacological interventions to minimal/no care controls.[9,10] The populations studied were children and adolescents up to 18 years of age for cessation and 25 years for prevention. The following main recommendations were provided by the USPSTF:

- For school-aged children and adolescents who have not started to use tobacco, primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents (Grade B, moderate certainty).[9]

The USPSTF determined current evidence was insufficient to assess the balance of benefits and harms of primary care-feasible interventions for the cessation of tobacco use among school-aged children and adolescents (Grade I, insufficient evidence).[9] Due to relatively few studies with small sample sizes available for review, it was unclear if the lack of effect observed with behavioral counseling and pharmacotherapy interventions was the result of intervention failure or lack of statistical power.[9]

After review, one smoking cessation guideline was excluded due to methodological limitations/low quality.

New Formulations:
None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[11]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Nicotine	Nicotrol	8/2019	Warnings and Precautions	Care should be taken not to spray the eyes while administering NICOTROL NS; In a small clinical study of 33 subjects, use of NICOTROL NS by smokers with chronic rhinitis and sinusitis was associated with irritant effects with no significant impairment in nasal condition; Pharmacokinetic studies in patients with moderate to severe renal impairment or moderate to severe hepatic impairment have shown decreased nicotine clearance. Consider dose reduction and monitoring patients for adverse events (such as nausea or dizziness) associated with elevated levels of nicotine; [caution in patients with] esophagitis, [active] gastric or [peptic ulcers]; Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately; Adverse reactions identified during post-marketing experience with the nicotine nasal spray formulation: chest pain, anaphylactic reaction, dysphagia
Bupropion hydrochloride	Zyban	7/2019	Adverse Reactions	hyponatremia

References:
1. Oregon Health Authority, Public Health and Health Systems Division Tobacco Cessation Coverage Standards. https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCOPREVENTION/Documents/ Published May 2014. Accessed November 30, 2020.
2. Claire R, Chamberlain C, Davey M-A, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. The Cochrane database of systematic reviews. 2020;3:CD010078.
3. Pearsall R, Smith DJ, Geddes JR. Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials. BMJ open. 2019;9(11):e027389.
4. Zhong Z, Zhao S, Zhao Y, Xia S. Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. Comprehensive psychiatry. 2019;95:152125.
5. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. The Cochrane database of systematic reviews. 2019;4:CD013308.
6. Lindson N, Klemperer E, Hong B, Ordonez-Mena JM, Aveyard P. Smoking reduction interventions for smoking cessation. The Cochrane database of systematic reviews. 2019;9:CD013183.
7. Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. The Cochrane database of systematic reviews. 2019;2019(10).
8. Leone FT, Zhang Y, Evers-Casey S, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. American Journal of Respiratory and Critical Care Medicine. 2020;202(2):e5-e31.
9. United States Preventative Services Task Force (USPSTF). Primary Care Interventions for Prevention and Cessation of Tobacco Use in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;323(16):1590-1598.
10. Selph S, Patnode C, Bailey SR, Pappas M, Stoner R, Chou R. Primary Care-Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2020;323(16):1599-1608.
11. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed 12/15/2020.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bupropion HCl	BUPROPION HCL SR	TAB ER 12H	PO	Y
nicotine	NICOTINE PATCH	PATCH DYSQ	TD	Y
nicotine	NICOTINE PATCH	PATCH TD24	TD	Y
nicotine polacrilex	NICOTINE GUM	GUM	BC	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZENGE	BC	Y
nicotine polacrilex	NICOTINE LOZENGE	LOZNG MINI	BC	Y
varenicline tartrate	CHANTIX	TAB DS PK	PO	Y
varenicline tartrate	CHANTIX	TABLET	PO	Y
nicotine	NICOTROL	CARTRIDGE	IH	N
nicotine	NICOTROL NS	SPRAY	NS	N

Appendix 2: New Comparative Clinical Trials

A total of 114 citations were manually reviewed from the initial literature search. After further review, all 114 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) ALL 1946 to November 30, 2020

1 smoking cessation.mp. or Smoking Cessation/ 39815
2 "tobacco use disorder".mp. or "Tobacco Use Disorder"/ 11593
3 nicotine gum.mp. /687
4 nicotine lozenge.mp. or "Tobacco Use Cessation Devices"/ 1929
5 nicotine patch.mp. or "Tobacco Use Cessation Devices"/ 2639
6 nicoderm.mp. /29
7 nicotine spray.mp. /49
8 bupropion.mp. or Bupropion/ 5061
9 varenicline.mp. or Varenicline/1983
10 1 or 2 /46173
11 3 or 4 or 5 or 6 or 7 or 8 or 9 /8881
12 10 and 11 /4749
13 limit 12 to (english language and humans and yr="2019 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) /130

Appendix 4: Key Inclusion Criteria

Population	Patients with tobacco use disorder
Intervention	Pharmacotherapy (nicotine replacement: patches, gum, lozenges, nasal spray, inhalation cartridges); bupropion, or varenicline with or without behavioral therapy
Comparator	Placebo or active comparator
Outcomes	Point prevalence abstinence/smoking cessation
Timing	Any study duration; literature search from August 2019 to November 2020
Setting	Inpatient hospital or outpatient clinics; worldwide

Smoking Cessation

Goal(s):

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

Length of Authorization:

- 3-6 months

Requires PA:

- Non-preferred drugs
- Nicotine replacement therapy (NRT) for more than 6 months in the absence of behavioral counseling
- Varenicline therapy for more than two x 12-week treatment regimens within 1 year or for patients less than 17 years of age

Covered Alternatives:

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

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

Approval Criteria		
5. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA for up to 6 months of initial treatment. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #8
6. Is the patient at least 17 years of age?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has patient had two or more treatment regimens of 12 weeks duration in the past year?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 additional weeks
8. Is the patient enrolled in a smoking cessation behavioral counseling program [e.g. Quit Line at: 800-QUIT-NOW (800-784-8669)].	**Yes:** Approve NRT for 6 additional months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *2/2021 (DE); 9/19; 7/16; 4/12*
Implementation: *(?);11/1/19; 8/16, 7/23/12*

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: Antidepressants

Date of Review: February 2021

Date of Last Review: July 2019
Dates of Literature Search: 04/01/2019 – 09/21/2020

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

Purpose for Class Update:
To evaluate new comparative evidence for antidepressant medications and to evaluate new Food and Drug Administration (FDA) indications for esketamine.

Research Questions:
1. What is the new comparative evidence for efficacy or effectiveness of antidepressants?
2. What is the new comparative evidence for safety or harms of antidepressants?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one antidepressant is more effective or associated with fewer adverse events?

Conclusions:
- In children and adolescents, there is limited evidence directly comparing efficacy or safety of various antidepressants. Selective serotonin reuptake inhibitors (SSRIs), as a class may improve response and functional status in adolescents with major depressive disorder (MDD), but are associated with an increased risk of adverse events (low quality evidence).[1] Guidelines from National Institute for Health and Clinical Excellence (NICE) recommend fluoxetine as an initial treatment option in children with moderate to severe depression unresponsive to psychotherapy.[2] Recommendations are made against the use of paroxetine, venlafaxine, or tricyclic antidepressants (TCAs) in children and adolescents.[2]
- In patients with MDD and a previous treatment failure, there was evidence that augmentation of an antidepressant with cariprazine, quetiapine, or ziprasidone improves symptom severity (based on moderate to high quality evidence).[3] Use of augmentation therapy with ziprasidone or cariprazine was associated with increased rates of treatment discontinuation.[3] There was no difference in efficacy upon augmentation with olanzapine, buspirone, or mirtazapine.[3]
- Preventative use of bupropion XL in adults with a prior history of seasonal affective disorder improved the number of patients who experienced a depressive episode during winter months compared to placebo (15% vs. 27%; relative risk [RR] 0.56, 95% CI 0.44 to 0.72; moderate quality evidence).[4]
- In adults with MDD, use of antidepressants (fluoxetine or TCAs) and benzodiazepines compared to antidepressants alone improved depression severity with less than 4 weeks of treatment (standardized mean difference [SMD] -0.25; 95% CI -0.46 to 0.03; I^2=35%; n=598), with no difference in depression severity with longer follow-up (based on low quality evidence).[5]

- There is moderate quality evidence that use of SSRIs after stroke may improve depressive symptoms and risk for depression but have no impact on disability.[6]
- There is insufficient evidence for use of traditional antidepressants in patients who are pregnant or postpartum.[7]
- NICE guidelines for treatment of general anxiety disorder in adults recommend SSRIs as an initial treatment option.[8] If initial treatment is ineffective, an alternative SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) is recommended.[8] In patients with panic disorder, antidepressants (including SSRIs, SNRIs or TCAs) are recommended if the disorder is long-standing or if the patient has not benefited from psychological interventions. If there is no benefit with initial treatment, an antidepressant from an alternative class should be considered.[8]
- Two randomized controlled trials (RCTs) evaluated use of esketamine in patients with MDD at high risk for suicide.[9,10] There is low quality evidence that esketamine does not decrease suicidality, but has a slight improvement in depression symptoms compared to placebo with a mean difference [MD] in the Montgomery-Asberg Depression Rating Scale (MADRS) of -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.[9,10] A 2 point improvement on MADRS may be associated with a clinically significant improvement.[11] There is insufficient evidence for other outcomes including suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

Recommendations:
- No PDL changes recommended based on current clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:
- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics and cost.
- Anti-depressants are designated preferred or part of the voluntary PDL.
- Safety edits are currently implemented for tricyclic antidepressant use in children, esketamine which is indicated for treatment resistant depression, and brexanolone which is indicated for post-partum depression.

Background:
Historically antidepressant medications have been categorized based on mechanism and chemical structure into first-generation (TCAs and MAOIs) and second-generation antidepressants (SSRIs, SNRIs, and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, post-traumatic stress disorder (PTSD), bipolar disorder, obsessive compulsive disorder, and anxiety disorders.[12] Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia, diabetic peripheral neuropathy, premenstrual dysphoric disorder, and smoking cessation.[12] All antidepressants have a box warning for suicide risk in young adults and can be associated a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Choice in antidepressant is typically dependent on patient preference and adverse effect profile as current evidence demonstrates little difference in efficacy between agents. Often second-generation antidepressants are recommended as first-line agents due to improved tolerability and decreased risk of adverse events compared to first-generation antidepressants. For example in patients with PTSD, first-line recommendations from the Veterans Administration and Department of Defense for pharmacotherapy include sertraline, paroxetine, fluoxetine, or venlafaxine in patients who are unable to access or choose not to

engage in trauma-focused psychotherapy.[13] For the treatment of moderate to severe depression in adults, guidelines from both NICE and the American Psychiatric Association (APA) recommend combination antidepressant and psychotherapy.[14] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects.[14] APA guidelines consider SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.[14] However, it's estimated that for major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[3] There is no consistent definition in the literature for treatment resistant depression, and there is little evidence to guide next steps in therapy after an initial treatment failure.[3] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent.

Goals of treatment for antidepressants typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. Some of the most commonly used rating-scales and thresholds include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[11] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52). [11] Values associated with remission and minimum clinically important differences for each of these scales vary. A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.[11] Typically, a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11]

In Medicaid, antidepressants are carved out of coordinated care organizations and paid for by fee-for-service. In the second quarter of 2020, there were over 133,000 patients with claims for an antidepressant medication. The most commonly prescribed medications are available as generics and included sertraline (15%), trazodone (14%), fluoxetine (11%), escitalopram (9%), duloxetine (9%), bupropion XL (8%), and citalopram (7%).

Methods:

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

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

New Systematic Reviews:

A recent AHRQ report evaluated pharmacologic and non-pharmacologic treatments for depressive disorders in children and adolescents.[1] For the majority of comparisons and outcomes, strength of evidence was graded as low or insufficient. Evidence was limited by high risk of bias for many included studies, small sample sizes, lack of reporting for harms, and potential for publication bias. Many outcomes and comparisons were evaluated in only single studies leading to unknown consistency. Overall, trials were of short duration and had a wide variety of reported tools to assess symptoms and diagnose depression in adolescents. This summary will focus on review of the available comparative evidence of pharmacologic treatment options. There were 29 studies (28 RCT and one nonrandomized trial) which addressed comparative effectiveness of therapies.[1]

- SSRIs compared to placebo: Fluoxetine and escitalopram may have a small statistical improvement in symptoms for adolescents with MDD based on results from single RCTs. As a class, SSRIs may be associated with improved response (risk difference [RD] 72/1000; 95% CI 2 to 124) and functional status (SMD 0.16; 95% CI 0.03 to 0.29), but increased risk of serious adverse events (RD 20/1000; 95% CI 1 to 440) and withdrawal due to adverse events (RD 26/1000; 95% CI 6 to 45).[1] Paroxetine may be associated with increased risk of suicidal ideation and behavior in adolescents. There was insufficient data for other drugs, but authors excluded inpatients and populations without MDD.[1]
- Psychotherapy compared to pharmacotherapy: There was low quality evidence from one RCT (n=220) that fluoxetine improved clinician-reported depression symptom scores compared to cognitive behavioral therapy (CBT) in adolescents with MDD over 12 to 16 weeks (SMD 0.66; 95% CI 0.39 to 0.93; absolute mean difference in the Children's Depression Rating Scale revised (CDRS-R) of 5.76; 95% CI 3.46 to 8.06).[1] There was insufficient evidence for other comparisons or efficacy outcomes including patient-reported symptoms, function, response or remission. Psychotherapy was associated with fewer treatment-emergent psychiatric adverse events compared to pharmacotherapy in adolescents with MDD over 12 weeks (RR 0.08; 95% CI 0.01 to 0.62; RD 100 fewer out of 1000 events; CI 40 to 160 fewer cases; low quality evidence).[1] Evidence on harms for other types of depression, comparisons, or outcomes including suicide-related adverse events was insufficient. Upon subgroup analysis, CBT was inferior to fluoxetine in patients with lower family income, severe baseline depression symptoms or comorbid attention deficit hyperactivity disorder (ADHD).[1] Other patient characteristics had no effect on outcomes, however subgroup analysis is limited by small sample sizes.
- Psychotherapy plus pharmacotherapy compared to psychotherapy alone: There was low quality evidence that combination therapy with CBT and fluoxetine improved clinician-reported depression scores (MD CDRS-R -8.27; 95% CI -10.59 to -5.95), remission (RD 210/1000; 95% CI 96 to 324 more cases), and functional status (MD in the Children's Global Assessment Scale of 6.6, 95% CI 3.23 to 9.97) in adolescents with MDD compared to CBT alone.[1] Clinician-reported depression scores were also improved with combination CBT and imipramine in school-refusing adolescents with MDD and comorbid anxiety based on low strength of evidence (MD CDRS-R -11.1; 95% CI -17.68 to -4.52).[1] Evidence for other efficacy outcomes, harms, or in other populations was graded as insufficient.
- Combination psychotherapy plus pharmacotherapy compared to pharmacotherapy alone: There was insufficient evidence for outcomes of clinician-rated depression symptoms, response, recovery, relapse, and function over 8 to 28 weeks.[1] Patient-reported depressive symptoms were improved with bupropion (MD in the Beck Depression Inventory [BDI] of -5.2; 95% CI -9.31 to -1.09) or fluoxetine combined with CBT, but showed no benefit for fluoxetine, sertraline or unspecified SSRIs (SMD -0.14; 95% CI -0.36 to 0.03; n=450; I^2=0%) based on low quality evidence.[1] Remission was improved with fluoxetine combined with CBT in MDD only (RR 1.61; 95% CI 1.05 to 2.46; RD 140/1000; 95% CI 19 to 261 more cases; low strength of evidence), but evidence was insufficient for other types of depression disorders.[1] Similarly, there was insufficient evidence of harms upon comparison of combination therapy to pharmacotherapy alone. Combination treatment was significantly improved in subgroups with more mild to moderate symptoms at baseline, higher treatment expectations, or comorbid ADHD.[1]
- SSRI versus SNRIs: There was insufficient evidence from 2 studies comparing duloxetine and fluoxetine in adolescents with MDD over 10 weeks.[1] Similarly, there was insufficient evidence to support conclusions of benefit or harms upon comparison of paroxetine and imipramine or fluoxetine and desvenlafaxine in adolescents with MDD over 8 weeks.[1]
- Treatment resistant depression: There was insufficient evidence for comparative interventions for treatment-resistant depression.[1]

A recent Cochrane review evaluated therapy for treatment-resistant depression in adults.[3] Nine of the 10 included studies were conducted in the outpatient setting, and all were located in high-income countries (4 in the United States).[3] Treatment resistance for this review was broadly defined as patients without response to at least 4 weeks of an adequately-dosed antidepressant.[3] Only one study evaluated patients with previous failure of at least 2 antidepressant from different classes, and 2 studies excluded participants inadequate response to 3 or more antidepressants.[3] Included patients were primarily female and, on average, 42 to 50 years of age.[3] Identified studies evaluated augmentation of current antidepressant therapy with a second drug over 8 to 12 weeks (either

mirtazapine, buspirone, or a second-generation antipsychotic).[3] Risk of bias was graded as either low or unclear based on lack of reported methods. About half of included studies had unclear risk for selection bias based on lack of reported methods for randomization or allocation concealment.[3] Attrition ranged from 14% to 41% without significant imbalances between groups.[3] Most studies used a last observation carried forward methodology to evaluate missing data.[3] Risk for selective reporting was rated as unclear or high for all except one study.[3] Results for primary efficacy and safety outcomes are summarized in **Table 1**. The most common reason for treatment discontinuation were inability to tolerate treatment (approximately 8% of all patients).[3]

Table 1. Antidepressant augmentation versus placebo in treatment-resistant depression[3]

Baseline therapy/ Duration	Augmenting agent	Outcome/Results	Quality of Evidence	Evidence Conclusion
SSRI/SNRI 1 RCT 12 weeks	mirtazapine	BDI-II (range 0 to 64): MD -1.7 (95% CI -4.03 to 0.63) Treatment discontinuation: RR 0.50 (95% CI 0.15 to 1.62) Quality of life (EQ-5D-5L): MD -0.01 (95% CI -0.06 to 0.04)	High High High	No difference between groups
SSRI 1 RCT 6 weeks	buspirone	MADRS: MD -0.3% from baseline (95% CI -9.48 to 8.88) Treatment discontinuation: RR 0.60 (95% CI 0.23 to 1.53)	Low	No difference between groups
Various antidepressants 1 RCT 8 weeks	cariprazine	MADRS: MD -1.5 (95% CI -2.74 to -0.25) Treatment discontinuation: RR 1.68 (95% CI 1.16 to 2.41); 81 per 1000 patients (95% CI 19 to 168) Response: RR 1.27 (95% CI 1.07 to 1.52); 103 per 1,000 (95% CI 27 to 199) Remission (MADRS ≤10): RR 1.07 (95% CI 0.86 to 1.33)	High Moderate Moderate Moderate	Statistical improvement in symptoms which did not achieve a minimum clinical difference vs. placebo; improvement in the proportion of patients with a response to treatment but not in remission. More patients discontinued treatment vs. placebo.
Fluoxetine 1 RCT 8 weeks	olanzapine	HAM-D: MD -7.9 (95% CI -16.76 to 0.96) MADRS: MD -12.4 (95% CI -22.44 to 2.36) Treatment discontinuation: RR 0.33 (95% CI 0.04 to 2.69)	Low Low Low	No difference between groups
Various antidepressants 3 RCTs	quetiapine	MADRS or HAM-D: SMD -0.32 (95% CI -0.46 to -0.18) Treatment discontinuation: RR 1.33 (95% CI 0.90 to 1.95) Response: RR 1.25 (95% CI 1.09 to 1.44); 110 per 1000 (95% CI 40 to 194) Remission MADRS score ≤8/HAM-D ≤ 7): RR 1.53 (95% CI 1.23 to 1.90); 123 per 1000 (95% CI 54 to 210) Quality of Life (Q-LES-Q-SF): MD 0.57 (95% CI -1.52 to 2.65)	High Moderate Moderate Moderate Moderate	Improved depression symptoms, patients with response and with remission, no difference in dropouts or quality of life
SSRI 2 RCTs 6 to 8 weeks	ziprasidone	HAM-D: MD -2.73 (95% CI -4.53 to -0.93) Treatment discontinuation: RR 1.60 (95% CI 1.01 to 2.55); 136 per 1,000 (95% CI 2 to 352) Response: RR 1.80 (95% CI 1.07 to 3.04); 145 more per 1,000 (95% CI 13 to 371)	Moderate Moderate Moderate	Improved depression symptoms and proportion of patients with a response (50% improvement), but remission did not achieve statistical significance. More patients

		Remission (clinician-rated): OR 1.46 (95% CI 0.75 to 2.86)	Moderate	discontinued treatment compared to placebo.

Abbreviations: BDI-II = Beck depression inventory II (range 0 to 63); CI = confidence interval; HAM-D = Hamilton Depression Rating Scale (range 0 to 52); MADRS = Montgomery Asberg depression rating scale (range 0 to 60); MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

A Cochrane review evaluating preventative antidepressant treatment for seasonal affective disorder (SAD) in adults identified 3 RCTs (n=1100) which evaluated efficacy of bupropion XL compared to placebo.[4] All trials enrolled adults with a history of seasonal affective disorder and no depressive symptoms at the time of enrollment.[4] Participants were primarily female (70%), white (89%) and had an average of 13 prior episodes of SAD.[4] Compared to placebo, fewer patients treated with bupropion experienced a depressive episode during the winter season (15% vs. 27%; ARR 12%; RR 0.56, 95% CI 0.44 to 0.72; moderate quality evidence).[4] The overall rate of adverse events (85% vs. 83%; RR 1.02, 95% CI 0.97 to 1.08) and discontinuation due to adverse events (9% vs. 5%; RR 1.68, 95% CI 0.74 to 3.79) was similar between groups.[4] However, patients treated with bupropion had a statistically increased chance for headaches (34% vs. 27%; RR 1.26, 95% CI 1.02 to 1.56), insomnia (20% vs. 13%; RR 1.46, 95% CI 1.10 to 1.93), and nausea (13% vs. 8%; RR 1.63, 95% CI 1.12 to 2.38) based on low to moderate quality evidence.[4] Evidence was limited by high attrition rates in all studies, and risk for reporting bias.[4] All three included studies were funded by the manufacturer of bupropion XL.[4]

A 2019 Cochrane review evaluated the effect of pharmacological and psychological continuation and maintenance treatments for persistent depressive disorder (illness duration >2 years).[15] Ten studies (n=840) were included, 7 RCTs and 3 non-randomized controlled trials.[15] Treatment interventions included both continuation (16 to 26 weeks) and maintenance (52 to 104 weeks) of pharmacotherapy and psychotherapy.[15] Overall, there was insufficient evidence comparing pharmacotherapy or antidepressant therapy when used as monotherapy or in combination compared to either therapy alone.[15] Evidence was primarily limited by small sample sizes, clinical heterogeneity, and moderate or high risk of bias. Risk of bias for non-randomized studies included risk of selective reporting, and for RCTs, included lack of blinding for outcome assessment and study funding. Five studies compared antidepressant medication to placebo. Compared to placebo, antidepressants reduced risk of relapse (33.8% vs. 13.9%; RR 0.41; 95% CI 0.21 to 0.79; I^2=54%; n=383; moderate quality evidence), but there was no difference between groups upon exclusion of studies with a high risk of bias.[15] Similarly, patients treated with antidepressants had lower symptom severity compared to placebo (MD in HAM-D –4.79, 95% CI –8.49 to –1.09; RCTs = 3; n = 333; I^2 = 60%).[15] Treatment discontinuation due to other reasons was similar compared to placebo (23.0% vs. 25.5%, RR 0.90, 95% CI 0.39 to 2.11; RCTs =4; n = 386; I^2 = 64%, low quality evidence).[15]

A recently updated Cochrane review evaluated evidence of combination antidepressants and benzodiazepines compared to antidepressants alone in adults with MDD.[5] Trials in the review included patients with comorbid anxiety and depression. Trials which evaluated concurrent psychosocial therapies were excluded. Primary outcomes included depression severity and acceptability of treatment. Secondary outcomes included response (50% improvement in severity scores), remission (usually defined as 7 or lower on HRSD or 11 or lower on MADRS), anxiety severity, insomnia severity, and adverse events.[5] Trials were at least 4 weeks in duration and outcomes were evaluated over several periods less than 4 weeks, 5-12 weeks, and more than 12 weeks.[5] There were 10 RCTs included in the review which evaluated fluoxetine (n=2) or a TCA (n=8).[5] Only one trial assessed treatment longer than 12 weeks. All trials were published prior to 2002 and had either high or unclear risk of bias for all risk of bias assessments.[5] Attrition was very high in 4 studies (34 to 41% of patients discontinuing treatment).[5] There was moderate quality evidence that depression severity was improved with combination treatment with less than 4 weeks of treatment (SMD -0.25; 95% CI -0.46 to -0.03; I^2=35%; n=598), with no difference in depression severity with longer follow-up (low quality evidence).[5] Similarly response (RR 1.34; 95% CI 1.13 to 1.58; I^2=0%; NNT 9; 95% CI 6 to 24) and remission (RR 1.39, 95% CI 1.03 to 1.90; I^2=2%) were improved with combination therapy compared to monotherapy at less than 4 weeks, but demonstrated no statistical difference between treatment groups with longer duration of therapy.[5] Acceptability of treatment evaluated

by treatment discontinuation for any reason was no different with combination therapy compared to antidepressant monotherapy (RR 0.76; 95% CI 0.54 to 1.07; I^2=36%; moderate quality evidence).[5] Patients prescribed combination therapy were less likely to discontinue treatment due to adverse events compared to monotherapy (RR 0.54, 95% CI 0.32 to 0.90; 64 dropouts [95% CI 38 to 107] vs. 119 dropouts with monotherapy per 1000 patients; moderate quality evidence), but were more likely to experience at least one adverse event (RR 1.12, 95% CI 1.01 to 1.23; moderate quality evidence).[5]

A Cochrane review evaluated impact of SSRIs compared to placebo or usual care on recovery after stroke.[6] Sixty-three trials (n=9168) were identified which evaluated symptom improvement within 1 year of their stroke.[6] The most common drugs evaluated included fluoxetine, paroxetine, citalopram and escitalopram.[6] The primary pre-specified analysis included only trials which had a low risk of bias (3 RCTs, n=3249).[6] In these trials, participants were not required to have depression symptoms upon enrollment. Overall, upon completion of treatment with an SSRI (74 to 180 days), there was no improvement in disability, neurological deficit score, death, or number of seizures based on moderate to high quality evidence.[6] Compared to placebo, SSRIs were associated with an improvement in depression severity (SMD -0.11; 95% CI -0.19 to -0.04; I^2=69%; moderate quality evidence) and risk of depression at the end of treatment (13.4% vs. 17.2%; RR 0.78, 95% CI 0.66 to 0.92).[6] Gastrointestinal adverse events were more common with treatment compared to placebo or usual care (RR 2.19; 95% CI 1.00 to 4.76; 234 per 1000 patients; 95% CI 107 to 508; moderate quality evidence).[6] Sensitivity analyses were conducted which evaluated outcomes for all identified trials regardless of risk of bias score. Twenty-six trials had sufficient data for meta-analysis and demonstrated a significant improvement in disability score compared to placebo with significant heterogeneity between trials (SMD 0.23, 95% CI 0.18 to 0.29; I^2=92%).[6] However, authors noted that studies with higher risk of bias (particularly lack of blinding for outcome assessors) were more likely to report favorable outcomes from treatment. Overall, they conclude that SSRIs do not affect disability or independence after stroke, but reduce risk of future depression and are associated with an increased risk of adverse gastrointestinal events.[6]

A systematic review conducted for the US Preventative Services Task Force evaluated interventions to prevent depression during pregnancy and the postpartum period.[7] Trials were included if they were at least 6 weeks in duration and evaluated recurrence rates of depression in high-risk patients.[7] Only 2 small studies evaluating the use of nortriptyline (n=58) and sertraline (n=22) were identified in the literature search.[7] Trials had mixed results and evidence for use of antidepressants was rated as insufficient overall.[7]

After review, the following systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria)[16-24] and wrong study design of included trials (e.g., observational, evaluation of non-drug therapy).[25,26]

New Guidelines:

High Quality Guidelines:

A 2011 NICE guideline on general anxiety and panic disorder in adults was updated in July 2019.[8] General recommendations for anxiety disorder include the following:[8]

- In patients with general anxiety disorder and marked functional impairment or in patients whose symptoms have not improved with psychoeducation or individual self-help, either drug treatment or individual high-intensity psychotherapy is recommended. Treatment choice is based on patient preference as there is no evidence that either option is more beneficial.
- Recommended initial drug treatments include SSRIs. Recommendations are made to assess for cocaine use when prescribing SSRIs and to avoid concurrent use of multiple concurrent serotonergic agents. Concomitant use of cocaine and citalopram may increase risk of bleeding which may be life-threatening.

- If initial treatment is ineffective, offer an alternative SSRI or SNRI. Anxiolytic effect may Treatment choice should consider potential for discontinuation syndrome (especially with paroxetine and venlafaxine), side effect profile, drug interactions, risk of suicide or overdose (especially venlafaxine), and prior treatment experience. Combination therapy with psychotherapy and drug therapy may be considered with failure of either therapy alone.
- If the patient is unable to tolerate SSRIs or SNRIs, consider offering pregabalin with careful evaluation for risk of abuse or dependence.
- Recommendations are made against use of benzodiazepines, except as a short-term measure during crisis, or antipsychotics in primary care.
- Referral to a specialist is recommended in patients with risk of self-harm, significant comorbidities, self-neglect, or inadequate response to pharmacotherapy or an SSRI.
- In patients with harmful comorbid substance use, treatment of the substance use disorder may significantly improve anxiety symptoms and is generally recommended before treatment of the anxiety disorder.

For patients with panic disorder, recommendations remain mostly unchanged from initial guidance in 2004.[8]

- Antidepressants (including SSRIs, SNRIs or TCAs) are recommended if the disorder is long-standing or if the patient has not benefited from psychological interventions. If there is no benefit with initial treatment, an antidepressant from an alternative class should be considered.
- Recommendations are made to consider a SSRI as initial treatment and either imipramine or clomipramine may be considered as alternative options if there is no improvement after 12 weeks.
- Benzodiazepines, sedating antihistamines, or antipsychotics are not recommended for panic disorder.

In 2019, NICE guidelines for identification and management of depression in children and adolescents age 5 to 18 years were updated.[2] Pharmacotherapy is not recommended except in combination with concurrent psychotherapy and should include careful, frequent monitoring and assessment (e.g., weekly contact for the first 4 weeks of treatment).[2] The following recommendations are based on symptom severity and age:[2]

- In patients with mild depression, antidepressants are not recommended. Treatment options include watchful waiting or psychotherapy.
- In patients with moderate to severe depression, initial treatment recommendations include psychotherapy. In patients unresponsive to psychotherapy, fluoxetine may be added. Fluoxetine can be offered to patients 12 to 18 years of age following multidisciplinary review if the patient is unresponsive to psychotherapy after 4-6 sessions. Fluoxetine can be cautiously considered in patients 5 to 11 years of age though there is limited evidence of efficacy in this age group. Fluoxetine is the only antidepressant in which clinical trial evidence demonstrates benefits outweigh risks.
- Intensive psychotherapy is recommended with or without medication therapy in patients with depression unresponsive to combined psychotherapy and fluoxetine, recurrent depression, or psychotic depression. Options for second-line antidepressant therapy include sertraline and citalopram. These medications should only be considered when the following criteria have been met:
    - Informed consent regarding likely risks and benefits of therapy
    - Sufficiently severe symptoms to justify another medication trial (e.g., weight loss, suicidal behavior)
    - Clear evidence of failure for combined psychotherapy and fluoxetine (including assessment of adherence to therapy)
    - Reassessment of diagnosis and cause of depression (including comorbidities)
    - Consultation with a child and adolescent psychiatrist
- Recommendations are made against the use of paroxetine, venlafaxine, or TCAs in children and adolescents due to unfavorable risk benefit ratio. Both paroxetine and venlafaxine lack an FDA indication in children and may be associated with severe adverse events including suicidal thoughts and behaviors.
- For children or adolescents with psychotic depression, augmentation with an antipsychotic may be considered though the optimal dose and duration of therapy are unknown. There is limited data on use of antipsychotics in MDD for children, and choice of antipsychotic is based primarily on evidence in other conditions (e.g., psychosis, schizophrenia).

- Drug therapy should be continued for at least 6 months after remission (defined as absence of symptoms for at least 8 weeks) in people with a response to treatment.

New Formulations or Indications:
In July 2020, esketamine nasal spray received an expanded indication for depressive symptoms in adults with MDD and acute suicidal ideation or behavior. Esketamine was previously approved for treatment-resistant depression. Approval was based on 2 identical double-blind, 4-week, multicenter RCTs in adults.[10] These trials enrolled a total of 456 patients from the United States, Europe, Asia, South Africa, South America, and Canada.[9,10] Participants had a diagnosis of MDD, suicidal ideation within the 24 hours prior to randomization with need for hospitalization due to imminent suicide risk, and a MADRS score greater than 28 indicating at least moderate depression.[9,10] Patients received comprehensive standard of care treatment including an initial 5 to 14 day hospitalization in a psychiatric unit.[9,10] Esketamine, administered twice weekly, was initiated upon enrollment with standard antidepressant optimization during the first 2 weeks of each trial.[9,10] Pharmaceutic standards of care could include either antidepressant monotherapy or an antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic or mood stabilizer).[9] Patients with clinically significant comorbidities were excluded from the studies (e.g., bipolar disorder, OCD, personality disorder, moderate to severe substance use disorder, psychotic disorder, renal or liver insufficiency, uncontrolled hypertension, history of malignancy, or clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic or metabolic disease).[9,10] The primary endpoint was change in depressive symptom severity evaluated with the MADRS score from baseline to 24 hours.[9,10] The key secondary outcome was symptom severity using the Clinical Global Impression of Severity of Suicidality - Revised scale (CGI-SS-r; range 0 to 6) which is a one-item, clinician-rated assessment of suicide severity.[9,10]

Overall, 78-89% of patients receiving esketamine and 82-83 % of patients receiving placebo completed 4 weeks of treatment, and about 72% of patients in each study completed the 90 day follow-up.[9,10] Baseline mean MADRS score was 40-41 indicating severe depressive symptoms, clinician-rated suicidality based on CGI-SS-r was moderate to extremely suicidal for 90-91% of patients.[9,10] Over 60% of patients in each study had a prior suicide attempt. In the first study, 28% had a recent attempt in the past month.[9] Common antidepressant therapy included venlafaxine, escitalopram, duloxetine, quetiapine, mirtazapine, and sertraline.[9,10] About 67-75% of patients received concomitant benzodiazepines, though use was not permitted within 8 hours of esketamine dosing.[9,10] Most baseline characteristics were balanced between groups. However, in the first study more males were randomized to esketamine compared to placebo (42% vs. 34%) and a slightly higher proportion of patients randomized to esketamine were prescribed antidepressant plus augmentation therapy compared to placebo (47% vs. 42%).[9] In the second study, the proportion of patients with a recent suicide attempt within the past 28 days at baseline differed between groups with more patients in the esketamine group with a recent suicide (31.6%) compared to placebo (21.2%).[10] A prior suicide attempt is a known risk factor for subsequent attempts which may indicate that patients randomized to treatment had more severe suicidality than those given placebo.

There was a substantial difference in MADRS from baseline to 24 hours for both esketamine and placebo groups. Patients given esketamine had mean improvements in MADRS of 16.4 (SD 11.95) and 15.7 (SD 11.56) points while patients randomized to placebo improved by 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.[9,10] The mean difference from placebo at 24 hours was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for Study 1 and 2, respectively. A 2-point change in MADRS may correspond with clinically meaningful improvements in symptoms. The difference from placebo was maintained at 4 weeks. Both placebo and esketamine groups had a decrease in acute suicidality (median 1 point improvement on CGI-SS-r from baseline to 24 hours), and there was no statistical difference compared to placebo indicating that hospitalization and standard therapy had a greater impact on acute suicidality.[9,10]

In general subgroup analyses were comparable to the overall treatment effect with little variability between groups. The largest variability in MADRS score was observed based on baseline MADRS scores greater or less than the median score and in patients with or without a prior suicide attempt with a trend toward

improved scores in patients with higher MADRS values or patients with a prior suicide attempt.[9] Subgroup analyses showed little difference between groups for the second study.[10]

The overall rate of suicide attempts during and after the study was low compared to current epidemiological data which authors attribute to the comprehensive clinical care and frequent follow-up required as part of the study. Nineteen percent (n=21) and 11% (n=13) of patients in studies 1 and 2, respectively, had a dose reduction due to intolerance.[9,10] In total, suicide-related adverse events (including suicidal ideation) occurred in 12 patients in the 4-week treatment period and were generally balanced between groups.[9,10] Eight suicide attempts occurred during therapy (4 in each group) on treatment.[9,10] During the 90 day follow-up period while on standard therapy, 10 patients had suicide attempts (7 with prior esketamine and 3 with prior placebo) during the follow-up period.[9,10] One patient, previously randomized to esketamine, completed suicide.[9] In most cases, patients with a suicide attempt after enrollment also had an attempt prior to enrollment.[9,10]

There is limited applicability to outpatient treatment, particularly during initiation of treatment in patients with suicidal ideation. The mean length of hospital stay in the second study was 21.6 days (SD 20.6) for patients receiving esketamine and 19.1 days (SD 19.6) for placebo indicating that the majority of the trial occurred during an inpatient stay.[10] Hospital duration was not reported in the first study. Both groups had a decrease in acute suicidality with no difference from placebo indicating that standard therapy, including hospitalization and greater clinical follow-up, likely continues to be the most effective treatment for suicidal symptoms. Psychotherapy was permitted, but less than 5% of patients received psychotherapy during the 4-week treatment phase.[10]

There is no evidence available from these studies which suggests that esketamine decreases suicidality, suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[27]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Escitalopram Levomilnacipran Paroxetine Vilazodone	Lexapro Fetzima Paxil CR Viibryd	8/2020 10/2019 9/2019 1/2020	Warnings/Precautions Boxed Warning	Clarification of warnings regarding risk of suicidal thoughts and behaviors in adolescents and young adults. Language was updated to include information on a pooled analyses of placebo-controlled trials which included approximately 77,000 adult patients and 4,500 pediatric patients. Patients 24 years of age and younger had greater risk of suicidal thoughts and behaviors compared to placebo. Close monitoring is recommended.
Escitalopram	Lexapro	8/2020	Warnings/Precautions	Use of escitalopram can cause activation of mania or hypomania. Language in the labeling was updated to recommend screening for personal or family history prior to use.
Nortriptyline	Pamelor	4/2019	Warnings/Precautions	Post-marking reports indicate a use of nortriptyline may unmask Brugada Syndrome, a disorder characterized by syncope, abnormal

				electrocardiographic (ECG) findings, and a risk of sudden death. Use is not recommended in patients with a history of Brugada Syndrome.
Clomipramine	Anafranil	5/2019	Warnings/Precautions	Clomipramine therapy has been associated with hyponatremia primarily as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Patients who are elderly or volume-depleted may be at greater risk for this adverse event. Monitoring is recommended.

Randomized Controlled Trials:

A total of 89 citations were manually reviewed from the initial literature search. After further review, all individual trials were excluded because of wrong study design (eg, observational or post-hoc analysis)[28-33] or comparator (eg, no control or placebo-controlled).[34-40]

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Appendix 1: Current Preferred Drug List

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

trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	PO	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	PO	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	PO	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	PO	Y
bupropion HBr	APLENZIN	TAB ER 24H	PO	V
bupropion HCl	BUPROPION XL	TAB ER 24H	PO	V
bupropion HCl	FORFIVO XL	TAB ER 24H	PO	V
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	PO	V
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	PO	V
clomipramine HCl	ANAFRANIL	CAPSULE	PO	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	PO	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	PO	V
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	PO	V
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	PO	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	PO	V
duloxetine HCl	CYMBALTA	CAPSULE DR	PO	V
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	PO	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	PO	V
esketamine HCl	SPRAVATO	SPRAY	NS	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	PO	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	PO	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	PO	V
isocarboxazid	MARPLAN	TABLET	PO	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	PO	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	PO	V
nefazodone HCl	NEFAZODONE HCL	TABLET	PO	V
paroxetine HCl	PAXIL	ORAL SUSP	PO	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	PO	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	PO	V
paroxetine HCl	PAXIL CR	TAB ER 24H	PO	V
paroxetine mesylate	PEXEVA	TABLET	PO	V
phenelzine sulfate	NARDIL	TABLET	PO	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	PO	V
selegiline	EMSAM	PATCH TD24	TD	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	PO	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	PO	V
vilazodone HCl	VIIBRYD	TAB DS PK	PO	V
vilazodone HCl	VIIBRYD	TABLET	PO	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	PO	V
amoxapine	AMOXAPINE	TABLET	PO	

brexanolone	ZULRESSO	VIAL	IV
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	PO
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	PO
trazodone HCl	TRAZODONE HCL	TABLET	PO

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to September 18, 2020

1	brexanolone.mp.	63
2	esketamine.mp.	204
3	escitalopram.mp.	2570
4	nefazodone.mp.	772
5	exp Antidepressive Agents, Second-Generation/	66705
6	exp Antidepressive Agents, Tricyclic/	31134
7	exp desvenlafaxine succinate/ or exp duloxetine hydrochloride/ or exp isocarboxazid/ or exp levomilnacipran/ or exp mirtazapine/ or exp phenelzine/ or exp selegiline/ or exp sertraline/ or exp tranylcypromine/ or exp vilazodone hydrochloride/ or exp vortioxetine/	11928
8	exp Depression/	120224
9	exp Depression, Postpartum/	5611
10	exp Suicide/	63293
11	exp Anxiety Disorders/	79634
12	exp Anxiety/	86039
13	exp Stress Disorders, Post-Traumatic/	32979
14	8 or 9 or 10 or 11 or 12 or 13	330834
15	1 or 2 or 3 or 4 or 5 or 6 or 7	102538
16	14 and 15	14061
17	limit 16 to (english language and humans and yr="2019 -Current")	268
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 equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	89

Appendix 3: Key Inclusion Criteria

Population	Patients with depression, anxiety, or post-traumatic stress disorder
Intervention	Antidepressants listed in **Appendix 1**
Comparator	Antidepressants listed in **Appendix 1** or other active comparator (e.g., psychological therapy)
Outcomes	Function, quality of life, symptoms, morbidity, mortality, significant adverse events
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Tricyclic Antidepressants

Goal(s):

- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

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 Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg	18
doxepin HCl	Depression Anxiety	150 mg	12

imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #5
5. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #6
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Esketamine (Spravato)

Goal(s):

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

Length of Authorization:

Up to 6 months

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to #10	**No:** Go to #5
5. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Does the patient have a history of substance abuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7

Approval Criteria		
7. Does the patient have treatment resistant depression (failure of two antidepressants which were each given for at least 6-8 weeks at FDA approved doses)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
8. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
9. Does the patient have documentation of any of the following: • Aneurysmal vascular disease or arterial venous malformation OR • Intracerebral hemorrhage OR • Pregnancy OR • Uncontrolled hypertension	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)
10. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No**: Go to #11
11. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (84 mg twice weekly for a maximum of 28 days)

P&T/DUR Review: 2/21(SS); 7/19 (KS)
Implementation: 8/19/19

Brexanolone (Zulresso)

Goal(s):

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

Length of Authorization:

- One time use only.

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
4. Is the patient an adult with moderate to severe post-partum depression?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

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: Non-Steroidal Anti-inflammatory Drugs

Date of Review: February 2021

Date of Last Review: March 2016
Dates of Literature Search: 01/01/2016 - 11/24/2020

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

Purpose for Class Update: To identify and present new evidence for the use of non-steroidal anti-inflammatory drugs (NSAIDs) since the last review in March of 2016. New formulations and approvals will also be discussed.

Research Questions:
1. Is there any new comparative effective evidence for NSAIDs based on meaningful outcomes (e.g., reduction in pain scores, improvement in function or disability, reduction in need for rescue therapy and quality of life)?
2. Is there any new comparative harms evidence differentiating NSAIDs?
3. Are there subpopulations of patients with for which specific NSAIDs may be more effective or associated with less harm?

Conclusions:
- There were 8 systematic reviews, 4 guidelines and 2 randomized controlled trials which met inclusion criteria for this review.

<u>PAIN</u>
- An Agency for Healthcare Research and Quality (AHRQ) review for therapies used in the treatment of chronic pain found NSAIDs to reduce pain and improve function, compared to placebo, in patients with osteoarthritis (OA) and inflammatory arthritis (e.g., rheumatoid arthritis) as demonstrated by the percentage of responders (number needed to treat [NNT] 10 for both indications).[1] Diclofenac was associated with a small, dose-dependent increased risk of cardiovascular (CV) events and diclofenac and celecoxib were associated with a moderate risk of coronary events. Ibuprofen was associated with a large risk of coronary events. Diclofenac, ibuprofen, and naproxen were associated with an increased risk of GI events.[1]
- The efficacy of celecoxib use in OA was the focus of a Cochrane review, which found high quality evidence that relative improvement in pain to be 12% higher in patients treated with celecoxib compared to placebo (standard mean difference [SMD] -0.22; 95% confidence interval [CI], -0.32 to -0.12; number needed to benefit [NNTB] 12).[2] There was also high quality evidence of a 12% (95% CI, 5% to 19%) relative improvement in physical function in patients treated with celecoxib compared to placebo (SMD -0.17; 95% CI, -0.27 to -0.07; NNTB 14).[2]
- A Cochrane review reported clinically significant improvements in pain in patients with rheumatoid arthritis (RA) treated with celecoxib compared to placebo (mean difference [MD] -11; 95% CI, -14.04 to -7.96; NNTB 4) and clinical improvement (NNTB 7)(moderate quality of evidence for both).[3] Fewer gastrointestinal (GI) ulcers occurred in patients treated with celecoxib compared to placebo.

Author: Kathy Sentena, PharmD

- A Cochrane review evaluated the efficacy of NSAIDs in the treatment of chronic back pain and found moderate quality of evidence that NSAIDs were slightly more effective than placebo in reducing pain (5.03 mm reduction on the 0-100 mm visual analog scale [VAS]). Differences were small and unlikely to be clinically meaningful.[4]
- A Cochrane systematic review and meta-analysis in adults with acute low back pain found moderate quality evidence that NSAIDs were more effective than placebo in pain reduction, demonstrated by a decrease of 7.29 mm on the 0-100 mm VAS, which is not considered clinically meaningful.[5]
- American College of Physicians (ACP) recommends NSAIDs first-line in patients with acute, subacute, and chronic low back pain based on moderate evidence and a strong recommendation.[6] The Veterans Affairs/Department of Defense (VA/DoD) guidelines on the treatment of low back pain also strongly recommend the use of NSAIDs for pain relief.[7] A National Institute for Health and Care Excellence (NICE) also recommends the use of NSAIDs for low back pain.[8]
- The American Society of Clinical Oncology (ASCO) recommends the use of NSAIDs for the treatment of chronic pain in adult cancer survivors based on intermediate evidence and moderate recommendation.[9]
- A Cochrane review of patients with acute soft tissue injuries found no clinically meaningful difference in efficacy between NSAIDs and acetaminophen or NSAIDs and opioids, based on moderate to high quality of evidence.[10]
- There was insufficient new evidence for evidence in specific subpopulations.

CYSTIC FIBROSIS

- In children with cystic fibrosis (CF) mean annual rate of change in percent predicted forced expiratory volume in one second (FEV_1) was increased by 1.32% (95% CI, 0.21% to 2.42%) in patients treated with NSAIDs (only ibuprofen studied) compared to -3.15% in the placebo group, based on moderate evidence.[11] Hospitalization occurred in 268 per 1000 patients treated with NSAIDs versus 440 per 1000 treated with placebo (OR 0.61 [95% CI, 0.37 to 1.01]) (moderate evidence).[11]

Recommendations:

- There is no new clinical evidence which warrants changes to the preferred drug list (PDL).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- This class was last reviewed in 2016 and at that time there were no changes to PDL. There was evidence that there was no difference between the efficacy of specific NSAIDs when treating low back pain or ankylosing spondylitis.
- NSAIDs on the PDL include: diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, naproxen, oxaprozin, salsalate, and sulindac.
- There are prior authorization (PA) criteria for non-preferred products and for ketorolac use beyond 5 days.

Background:

NSAIDS are commonly used over the counter and prescription pain relievers that also have antipyretic and anti-inflammatory properties. NSAIDs are used for many types of pain, including back pain, arthritis pain and soft tissue injuries. NSAID use is associated with adverse events including gastrointestinal bleeds, peptic ulcer disease, renal disease, hypertension and increased risk of myocardial infarction (MI).

Efficacy of NSAIDs are measured by outcomes of pain intensity. Measurements of pain intensity are done by administration of validated measurement scales such as the visual analog scale (VAS). The VAS measures pain intensity based on a scale of either 0-10 or 0-100. The suggested minimally clinical important difference (MCID) for the VAS 0-100 mm is 13 mm.[10] Measurement of disability is also used to define efficacy of NSAIDs. Commonly used measures of disability are: the Western Ontario and McMaster Universities Arthritis Index (WOMAC) physical function score and pain score and Roland Morris Disability Questionnaire (RMDQ). The WOMAC is used for patients with hip or knee OA and measures function, pain and stiffness in the previous 48 hours, with the with higher scores indicative of functional difficulty.[12] The MCID for the WOMAC physical function score is 2 points on the 100 point scale.[12] The RMDQ measures the impact of low back pain on daily physical activities with a 24 point scale, with higher scores indicative of severe disability.[13] Changes of 2-3 points in the RMDQ have been reported by systematic reviews as the MCID.[14]

Total expenditures in this drug class account for a small portion of quarterly prescription costs for the Oregon Health Plan (OHP). Ninety-eight percent of utilization is for preferred NSAID products, most commonly ibuprofen.

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

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

New Systematic Reviews:

PAIN
AHRQ – Nonopioid Pharmacologic Treatment for Chronic Pain
A high quality systematic review and meta-analysis was done by AHRQ to determine the efficacy of therapies for the treatment of chronic pain.[1] There were 184 randomized controlled trials (RCTs) which met inclusion criteria, which included the following oral therapies: NSAIDs, antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anticonvulsants, acetaminophen, muscle relaxants and memantine. Topical therapies, related to NSAIDs, that were included in the review were various diclofenac formulations. Studies using NSAIDs for pain were for the following indications: neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis (e.g., rheumatoid arthritis), low back pain, chronic headache and sickle cell disease. Patients were a mean age of 59 years with a weighted mean pain score of 6 on a 10-point scale. Studies were divided into 3 treatment time frames: 1) short duration (3 to 6 months), intermediate (6 to 12 months) and long-term (12 months or more). Fifty-six studies evaluated the efficacy and safety of NSAIDs. Pain was assessed via the visual analog scale (0-10 points) or the numerical rating scale (NRS) (0-10 or 0-100 point scale).[1] Primary pain response, defined as 30 or more percent improvement (reduction), in pain score. Evidence was graded as high, moderate, low or insufficient. The degree of pain control was divided into 3 groups: small effect, moderate effect, and large effect (**Table 1**). Evidence related to the use of NSAIDs will be presented.

Table 1. AHRQ Definition of Effect Size of Therapies Used for Chronic Pain[1]

Effect Size	Mean Difference	Standard Mean Difference	Relative Risk/Odds Ratio
Small Effect	0.5 to 1.0 points on 0 to 10-point scale 5 to 10 points on 0 to 100-point scale	0.2 to 0.5	1.2 to 1.4
Moderate Effect	>1 to 2 points on 0 to 10-point scale >10 to 20 points on 0 to 100-point scale	>0.5 to 0.8	1.5 to 1.9
Large Effect	>2 points on a 0 to 10-point scale >20 points on a 0 to 100-point scale	>0.8	≥2.0

Improvements in both pain and function were demonstrated with oral NSAIDs (e.g., celecoxib, diclofenac, ibuprofen, meloxicam, and naproxen) compared to placebo in participants with OA in the short term, based on moderate strength of evidence and high strength of evidence, respectively. NSAIDs reduced pain more than placebo (27 RCTs; MD -0.73; 95% CI, -0.84 to -0.62) and more patients responded to NSAIDs versus placebo (15 RCTs, relative risk [RR] 1.23 (95% CI, 1.18 to 1.31; absolute risk reduction [ARR] 10%/number needed to treat [NNT] 10).[1] Results were maintained with celecoxib in the intermediate term. Average pain severity was reduced with topical diclofenac to a small effect in patients with OA (4 RCTs; MD -0.58; 95% CI, -0.81 to -0.35) (moderate strength of evidence). There was insufficient evidence to differentiate pain response between NSAID therapies or doses in patients with OA; however, diclofenac moderately improved pain and function more than celecoxib in the short term (MD -12.2; 95% CI, -22 to -2.2).[1] There was insufficient evidence for the use of NSAIDs in chronic headache, sickle cell disease and low back pain to draw strong conclusions.

Patients with RA treated with short term oral NSAIDs versus placebo demonstrated small to moderate improvements in pain severity and function based on moderate evidence. Pain severity was reduced more with NSAIDs compared to placebo by a MD of -0.97 (95% CI, -1.33 to -0.74) and function (SMD -0.34, 95% CI, -0.51 to -0.20).[1] Moderate improvements in pain response in patients with RA or ankylosing spondylitis treated with NSAIDs compared to placebo, was also demonstrated (RR 1.28; 95% CI, 1.03 to 1.60; ARR 10%/NNT 10).[1]

Serious adverse events were low for all NSAIDs. Short term use of NSAIDs was associated with a higher incidence of discontinuations due to adverse events, with a small increase in those taking ibuprofen or diclofenac and moderate increase for those taking naproxen (moderate quality of evidence).[1] Diclofenac was associated with a small increased risk of any CV event, most commonly in the first 6 months and with higher doses. Diclofenac and celecoxib were associated with an increased risk of major coronary events to a moderate degree and to a large increase was seen with ibuprofen. There were no differences in CV events, in the intermediate and long term, between nonselective NSAIDs and celecoxib (moderate quality of evidence). There was a moderate increase risk in gastrointestinal (GI) events in patients taking diclofenac and a large increase in those patients taking ibuprofen or naproxen, more often reported in the first 6 months of treatment. Diclofenac and naproxen were found to have a large increase in risk of hepatic harm in the intermediate term based on moderate to low quality of evidence.

In summary, NSAIDs resulted in small to moderate improvements in pain and function in the short term, when compared to placebo. Longer studies and head to head comparisons are needed to further determine benefit of chronic use.

Cochrane - Celecoxib for Osteoarthritis

A 2017 Cochrane review evaluated the efficacy and safety of celecoxib use in adult patients with OA.[2] Trials involving OA of the hip, knee or both were included. Thirty-six trials (n= 17,206) were included that studied celecoxib 200 mg/day compared to naproxen, diclofenac or placebo. The mean duration of osteoarthritis was 7.9 years and a mean age of 62. Studies lasted up to 52 weeks.[2] Pain was measured by the WOMAC score, which ranges from 0-500, with 0 being indicative of no pain. The WOMAC physical function score was used to measure physical limitation. A majority of studies had high attrition bias and 30% had selective reporting. All studies were supported by industry.

Self-reported absolute improvement in pain based on the WOMAC score was 3% (95% CI, 2% to 5%) higher for celecoxib compared to placebo based on high quality of evidence.[2] Relative improvement in pain was 12% higher in patients treated with celecoxib compared to placebo (SMD -0.22; 95% CI, -0.32 to -0.12; NNTB 12) (high quality evidence). Physical function was 4% (95% CI, 2% to 6%) absolutely improved in patients treated with celecoxib based on the WOMAC physical function score (high quality of evidence). There was a 12% (95% CI, 5% to 19%) relative improvement in physical function in patients treated with celecoxib compared to placebo (SMD -0.17; 95% CI, -0.27 to -0.07; NNTB 14) based on high quality of evidence.[2] There was no difference in the number of patients who withdrew due to adverse events.

Two trials compared celecoxib to naproxen 1000 mg/day and diclofenac 100 mg/day. Pooled data reported a 5% absolute improvement and 11% relative improvement with celecoxib compared to NSAIDs; however, results were inconclusive (MD -4.52; 95% CI, -10.65 to 1.61).[2] There was moderate quality of evidence from 1 trial that celecoxib was associated with a relative improvement in physical function more than naproxen (MD -6.0; 95% CI, -11.40 to-0.60; p=0.03; NNTB 9).[2]

There is limited evidence that celecoxib may decrease pain and improve physical function compared to placebo; however, differences were small and unlikely to be clinically significant. There is insufficient evidence to make strong conclusions on celecoxib and NSAID comparisons.

Cochrane – Celecoxib for Rheumatoid Arthritis

The efficacy of celecoxib, compared to placebo or traditional NSAIDs, for the treatment of RA was the focus of a 2017 Cochrane review.[3] Eight RCTs (n=3988) lasting from 4-24 weeks were included in the review. Seventy-three percent of patients were women with an average duration of RA of 9.2 years.[3] Five of the 8 trials were sponsored by industry and the evidence was considered to be of low to moderate quality. Clinical improvement was accessed by the American College of Rheumatology 20 (ACR20) score. Pain was assessed by the VAS pain scale, scores ranging from 0-100, with 0 indicating no pain.

Celecoxib (200-400 mg/day) was compared to placebo in 2 trials. Celecoxib use resulted in a 15% absolute improvement (assessed by ACR20) over placebo and 53% of patients had relative improvement (NNTB 7) based on moderate quality of evidence.[3] Mean pain scores were 60 for placebo and 49 for celecoxib (MD -11; 95% CI, -14.04 to -7.96; NNTB 4) (moderate quality of evidence). There was moderate evidence that celecoxib improved ACR20 scores more than traditional NSAIDs by 4% absolute improvement and 10% relative improvement; however, results were not statistically significant.[3] Pain scores were not statistically or clinically different between celecoxib and traditional NSAIDs based on the VAS scale (MD -1.59; 95% CI, -3.83 to 0.65) based on moderate quality of evidence. Traditional NSAIDs resulted in a risk of GI ulcers >3mm in 155 per 1000 patients compared to 34 per 1000 patients treated with celecoxib (RR 0.21; 95% CI 0.14 to 0.32) (moderate quality of evidence).[3] There was moderate quality of evidence that the incidence of celecoxib withdrawals was lower than traditional NSAIDs (RR 0.73; 95% CI, 0.62 to 0.86) based on 6 trials. There was insufficient evidence to determine CV risk.

Use of celecoxib resulted in significant clinical improvement compared to placebo in absolute improvement. Improvement in pain scores were marginally more improved with celecoxib compared to traditional NSAIDs and there were fewer risks of GI ulcers in patients treated with celecoxib compared to traditional NSAIDs.

Cochrane – NSAIDs for Chronic Low Back Pain

A 2016 Cochrane review evaluated the efficacy of NSAIDs for the treatment of non-specific chronic low back pain.[4] Thirteen studies (n=4807) were included and 10 were considered to have low risk of bias. In placebo controlled trials the most commonly studied NSAID was naproxen.[4] Overall risk of bias was low; however, only 2 trial had a low risk of reporting bias.

While evidence was of low quality for most outcomes, there was moderate quality of evidence that NSAIDs resulted in a greater change in pain intensity from baseline with a reduction in 5.03 mm, as measured by VAS (scale 0-100), compared to placebo.[4] There was a similar reduction in disability, as measured by the Roland Morris Disability Questionnaire (RMDQ), from baseline between groups with a 0.41 point reduction reported in the NSAID group compared to placebo based on moderate quality of evidence.[4] There was insufficient comparative efficacy evidence between different NSAIDs.

In summary, NSAIDs were only slightly more effective than placebo for the treatment of low back pain and the magnitude of effect was small and did not meet the threshold for being a clinically meaningful change.

Cochrane – NSAIDs for Acute Low Back Pain

A 2020 systematic review and meta-analysis was done by Cochrane on the use of NSAIDs for acute low back pain to update a 2008 review.[5] Thirty-two trials, enrolling 5,356 adult patients, were included. Trial durations lasted from 1 day to 6 months. NSAIDs included in the trial were: diclofenac, ibuprofen, piroxicam, naproxen, indomethacin, diflunisal, meloxicam, ketorolac, aspirin, and several preparations that are not available in the US (dipyrone, tenoxicam, lornoxicam, aceclofenac, felbinac, etofenamat, dexketoprofen, phenylbutazone, and felbinac foam).[5] Nine trials were placebo comparisons, 3 trials were NSAIDs versus acetaminophen, 17 trials compared different NSAIDS, 4 trials compared NSAIDs to other drugs (e.g., acetaminophen and codeine, tramadol, meptazinol [not available in the US]), and 7 trials compared NSAIDs to non-drug treatments.[5] Follow-up more than 3 weeks was studied in 5 trials, all other trials were of shorter duration. Fourteen of the studies were sponsored by industry. Approximately half of the studies were deemed to be at low risk of bias.

There was moderate quality of evidence that NSAIDs were more effective than placebo, in studies lasting less than 3 weeks, for the outcome of pain intensity (as measured by the VAS 0-100 scale). Pain intensity scores were 7.29 mm (95% CI, 10.98 to 3.61) lower compared to placebo.[5] Disability was measured by the RMDQ, which scores range from 0-24 and lower is better. Disability scores were lower by 2.02 points (95% CI, 2.89 to 1.15 points lower) for NSAIDs compared to placebo based on high quality evidence.[5] There was moderate quality of evidence that disability, as measured by the Oswestry Disability Index (ODI) which has scores from 0-50 with lower scores are better, found a mean difference of 7 points (95% CI, -13.15 to -0.85) benefitting NSAIDs compared to selective COX-2 inhibitors.[5] A second study found no difference in disability between valdecoxib and diclofenac, based on moderate quality evidence.

For short-term pain reduction in patients with acute low back pain, the use of NSAIDs reduced pain approximately 7% more than placebo and with an approximate 8% reduction in disability. NSAIDs may also reduce disability more than COX-2 inhibitors but there was no definitive differences in pain reduction.

Cochrane – Oral NSAIDs versus Other Oral Analgesic Agents for Acute Soft Tissue Injury

A 2020 Cochrane review evaluated the effectiveness of selective and non-selective NSAIDs for the treatment of soft tissue injuries compared to other therapies.[10] An acute soft tissue injury was defined as sprain, strain, or contusion of a joint, ligament, tendon, or muscle occurring within 48 hours of the study. The most common injury was ankle strains. Studies included the following NSAIDS: ibuprofen, valdecoxib, indomethacin, naproxen, diflunisal and diclofenac.[10] Comparative therapies included acetaminophen, opioid, opioid + acetaminophen, or complementary and alternative medicine. Twenty studies, including 3305 participants, were included in the review.[10] Sixty percent of participants were male and a majority of participants were young adults, with three studies including only children. Most studies were at low risk of bias. Results for the efficacy and harms findings are presented in **Table 2**. Overall, there were no clinically meaningful difference between NSAIDs and acetaminophen or NSAIDs and Opioids.

Table 2. Evidence for the Use of NSAIDs for Acute Soft Tissue Injuries[10]

Comparison	Outcome	Result	Strength of Evidence
NSAIDs compared to Acetaminophen	Pain at <24 hours based on VAS 0-100 mm (follow-up 1-2 hours)	Mean pain score was reduced by -12 to -19 mm from baseline in the acetaminophen group and by an additional 0.12 mm lower (95% CI 2.27 lower to 2.03 higher) in the NSAID group	High *Change in VAS is not clinically significant – no difference between groups*
	Pain at days 1-3 based on VAS 0-100 mm (follow-up 2-3 days)	Mean pain score was reduced by -12.7 to -18.3 mm from baseline in the acetaminophen group compared to 1.5 mm higher (95% CI, 0.91 lower to 3.91 higher) in the NSAID group	High *Change in VAS is not clinically significant – no difference between groups*
NSAID compared to Opioids	Pain at <24 hours based on VAS 0-100 mm (follow-up 1 hour)	The mean pain score for those taking opioids ranged from 13 to 27.7 mm and the mean pain score was 0.49 mm lower (95% CI, 3.05 lower to 2.07 higher)	Moderate *Change in VAS is not clinically significant– no difference between groups*
	Gastrointestinal adverse events (follow up 2 hours to 14 days)	Opioid: 205 per 1000 patients NSAID: 98 per 1000 patients RR 0.48 (95% CI, 0.36 to 0.62)	Moderate *Opioids were associated with more gastrointestinal events than NSAIDS*
	Neurological (follow up 2 hours to 14 days)	Opioid: 203 per 1000 patients NSAID: 81 per 1000 patients RR 0.40 (95% CI, 0.30 to 0.53)	Moderate *Opioids were associated with more neurological events than NSAIDS*
Abbreviations: CI – confidence interval; NSAID – non-steroidal anti-inflammatory; RR – relative risk; VAS – visual analog scale			

FEBRILE SEIZURES

Cochrane – Prophylactic Drug Management for Febrile Seizures in Children

The focus of a 2017 Cochrane review was the study of antiepileptics and antipyretics or other treatments for the prophylactic treatment of febrile seizures.[15] Thirty RCTs were included in the review. The evidence for the use of NSAIDs will be presented.

The use of intermittent oral ibuprofen compared to placebo was associated with no effect on the outcome of recurrent seizures at 6 months (RR 1.11; 95% CI, 0.69 to 1.81) (high quality of evidence).[15] Similar results were reported for the outcome of recurrent seizures at 12 months (RR 0.95; 95% CI, 0.63 to 1.43) based on high quality evidence. Recurrent seizures occurred in 325 per 1000 patients treated with ibuprofen at 24 months compared to 387 per 1000 patients treated with placebo (RR 0.84; 95% CI, 0.59 to 1.19)(high strength of evidence).[15] Intermittent rectal diclofenac was found to be similar to placebo for the outcome of recurrent seizures at 6 months (RR 0.80; 95% CI, 0.42 to 1.55) based on high strength of evidence. There was also no difference at months 12, 18 and 24.[15]

Overall there was no evidence to support the use of ibuprofen or diclofenac to prevent recurrent febrile seizures in children.

CYSTIC FIBROSIS

Cochrane – Oral NSAID Drug Therapy for Lung Disease in Cystic Fibrosis

A 2019 Cochrane review updated previous findings related to the use of NSAIDs in in patients with CF to determine if there is a protective effective from pulmonary decline and morbidity.[11] Four trials met inclusion criteria; 3 trials compared ibuprofen to placebo and 1 trial compared piroxicam to placebo. Patients were 5-39 years of age.[11]

There was moderate quality of evidence that the mean annual rate of change in percent predicted FEV_1 was increased by 1.32% (95% CI, 0.21 to 2.42) in patients treated with NSAIDs (only ibuprofen studied) compared to -3.15% in the placebo group.[11] In participants who were under the age of 13 years, the mean annual rate of change in percent predicted FEV_1 was 1.41% (95% CI, 0.03% to 2.80%) compared to -3.32% in the placebo group (moderate quality of evidence).[11] The mean annual rate of change in percent predicted FEV_1 in participants 13 years and older was 0.75% (95% CI, 1.02% to 2.52%) higher in those treated with NSAIDs compared to -3.18% in those treated with placebo.[11] The mean annual rate of change in percent predicted forced vital capacity (FVC) was 1.27% (95% CI, 0.26% to 2.28%) higher compared to placebo value of -2.65%, based on moderate evidence.[11] In participants under 13 years of age, the mean annual rate of change in percent predicted FVC was higher in those treated with NSAIDs compared to placebo, 1.32% (95% CI, 0.04% to 2.60%) versus -2.03% (moderate evidence).[11] In patients over 13 years old, the mean annual rate of change in percent predicted FVC was 0.78% (95% CI, 0.71% to 2.27%) compared to placebo change of -2.03%, based on moderate evidence.[11] The number of patients with at least 1 hospitalization was less in patients treated with NSAIDs compared to placebo, 268 per 1000 versus 440 per 1000 (OR 0.61 (95% CI, 0.37 to 1.01) (moderate evidence).[11]

There was no significant difference in the number of hospitalizations in patients treated with piroxicam compared to placebo, 7 versus 11.[11] No lung studies were conducted in the piroxicam trial.

In summary, evidence from a limited number of trials found moderate evidence that NSAIDs are effective in increasing FEV1, FVC and reduction in the number of hospitalization days.

GYNECOLOGY

Cochrane – NSAIDs for Heavy Menstrual Bleeding

A 2019 Cochrane review evaluated the use of NSAIDs in achieving reduction in menstrual blood loss (MBL) in women of reproductive years with heavy menstrual bleeding (HMB).[16] Nineteen RCTs were identified for inclusion. Patients were 18 to 55 years.[16] The most commonly studied NSAID was mefenamic acid and naproxen. HMB was measured by the alkaline hematin method, which measures menstrual blood loss.

For many comparisons there was only low quality of evidence available. In a small study comparing NSAIDs to ethamsylate (also spelled etamsylate) the mean MBL was 42.88 mL/cycle lower (95% CI, 86.25 lower to 0.5 mL/cycle higher) than those patients treated with ethamsylate (moderate quality of evidence).[16] In patients treated with NSAIDs the MBL was 45.06 mL/cycle higher (95% CI, 18.73 to 71.39 higher) compared to danazol based on moderate strength of evidence.[16] The number of days bleeding was 1.03 higher in patients treated with NSAIDs compared to danazol (moderate strength of evidence).[16] There was moderate quality of evidence that the use of NSAIDs resulted in 0.41 fewer days' bleeding (95% CI, 0.95 lower to 0.13 higher).[16] Only low quality evidence was available for the following comparisons and therefore, no strong conclusions could be made: NSAIDs versus placebo, NSAIDs versus tranexamic acid, NSAIDs versus progesterone-releasing intrauterine system, NSAIDs versus oral contraceptives, and mefenamic acid versus naproxen.

Limitations include small study size and unclear risk of bias for allocation concealment in most studies.

After review, 38 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).[17–25, 26–35, 36–45, 28,46–55]

New Guidelines:

High Quality Guidelines:

NICE – Low Back Pain and Sciatica: Assessment and Management

NICE updated guidance on the treatment of back pain and sciatica in 2016.[8] Patients should be encouraged to incorporate non-pharmacological interventions into low back pain management strategies. The main treatments used in the management of back pain, with or without sciatica, include NSAIDs, acetaminophen, opioids, anticonvulsants, antidepressants and muscle relaxants (**Table 3**).[8] NICE recommends against the use of gabapentinoids, other antiepileptics, oral corticosteroids, SSRIs, SNRIs, TCAs or benzodiazepines due to lack of evidence of benefit and the potential to cause harm.[8] If patients are currently using these medications the risks and benefits should be discussed and consideration should be given to drug discontinuation.

Table 3. NICE Pharmacotherapy Recommendations for Low Back Pain and Sciatica[8]

Pharmacotherapy	Considerations	Evidence
Sciatica		
NSAIDs	• Use lowest effective dose for shortest period of time • Consider risk for gastrointestinal, liver and cardio-renal toxicity and the person's risk factors including age	- Limited evidence of benefit - Evidence is combined for patients with or without sciatica (see below under low back pain)
Opioids	• Do not offer for chronic management	- Not reported
Low Back Pain		

NSAIDs	• Consider use of NSAIDs for low back pain management taking into account risk for gastrointestinal, liver and cardio-renal toxicity and the person's risk factors including age • Use lowest effective dose for the shortest period of time • Consider clinical assessment, management of risk factors on an ongoing basis and use of gastroprotective treatment	- Most evidence is of low quality - Mean change in pain scale was 0.9 points on scale of 1-10 compared to placebo
Opioids	• Do not routinely use opioids for acute or chronic low back pain • Consider weak opioids, with or without acetaminophen, for managing acute back pain only in patients who have contraindications to NSAIDs	- Moderate quality of evidence - Changes in pain intensity was 0.59 points lower than placebo (pain scale of 0-10)
Acetaminophen	• Not recommended as a single agent	- All evidence is of low quality

American College of Physicians – Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain

In 2017 ACP published guidelines for the treatment of acute, subacute and chronic low back pain.[6] The guideline recommendations are based on a systematic review done by AHRQ, which is considered a high quality source for evidence. Recommendations are graded from strong to weak, based on quality of evidence of low, moderate or high. Acetaminophen, NSAIDs, systemic corticosteroids, opioids and skeletal muscle relaxants, benzodiazepines and antidepressants, as well as non-pharmacotherapy interventions, where included in the review.[6] Clinical outcomes considered where reduction or elimination of low back pain, improvement in function, improvement in health-related quality of life, reduction in disability and return to work, patient satisfaction, number of back pain episodes and time between episodes and adverse events.

ACP strongly recommends the use of NSAIDs or skeletal muscle relaxants if pharmacotherapy is recommended based on moderate quality of evidence (**Table 4**).[6] Evidence founds small improvements in pain intensity compared to placebo; however, no difference in likelihood of achieving pain relief between NSAIDs and placebo was demonstrated in several RCTs. A small increase in function was found with NSAIDs versus placebo, based on low-quality of evidence.[6] There was no difference between specific NSAIDs in pain relief in patients with acute back pain, based on moderate evidence. Low quality evidence found no difference between NSAIDs and COX-2 inhibitors.[6] Patients with chronic low back pain who have not found had adequate pain relief with non-pharmacologic options, should be considered for NSAID therapy as a first-line option, or tramadol or duloxetine as a second-line therapy (moderate quality of evidence, weak recommendation).[6] Opioids should only be considered for patients who fail previously recommended therapy (moderate evidence, weak recommendation).

Table 4. Pharmacological Treatment Benefits of NSAIDs versus Placebo in Acute or Subacute Low Back Pain[6]

Outcome	Magnitude of Effect	Strength of Evidence	Data
Pain	Small (pain intensity) No effect (pain relief)	Moderate	WMD -8.39 (95% CI, -12.68 to -4.10; P>0.10) (scale of 0-100)
Abbreviations: CI – confidence interval; WMD – weighted mean difference			

VA/DOD – Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain

An update to the 2007 guidelines for the treatment of low back pain was published in 2017 by the VA/DOD.[7] Guidance published by the VA/DOD meets DURM inclusion criteria as part as one of our high quality sources. A literature search ranged from January 2006 through September 2016. Thirty-three treatment recommendations were made, 12 for pharmacologic therapy (**Table 5**). The strength of the recommendations ranged from weak to strong, based on quality of evidence.

There was only one recommendation pertaining to NSAIDs (**Table 5, #1**).[7] No clear difference in pain relief was found between the specific NSAIDs and no difference in pain relief was found between traditional NSAIDs and COX-2 NSAIDs. Evidence for the use of NSAIDs to improve function and reduce disability was inconclusive. COX-2 NSAIDs were found to have fewer adverse events than traditional NSAIDs.[7] Increased risk of CV events is associated with traditional and COX-2 NSAIDs.

Table 5. VA/DOD Pharmacologic Treatment Recommendations for Low Back Pain[7]

Recommendations	Strength
1. For patients with acute or chronic low back pain, treatment with **nonsteroidal anti-inflammatory drugs**, with consideration of patient-specific risks is recommended.	Strong
2. For patients with chronic low back pain, treatment with **duloxetine**, with consideration of patient-specific risks is recommended.	Weak
3. For patients with acute low back pain or acute exacerbations of chronic low back pain, offer a non-**benzodiazepine muscle relaxant** for short-term use.	Weak
4. For patients with chronic low back pain, offer a **non-benzodiazepine muscle relaxant.**	Weak
5. For patients with low back pain, **benzodiazepines** are not recommended**.**	Strong
6. For patients with acute or chronic low back pain with or without radiculopathy, the use of **systemic corticosteroids** (oral or intramuscular injection) are not recommended.	Strong
7. For patients with low back pain, initiating **long-term opioid therapy** is not recommended. For patients who are already prescribed long-term opioid therapy, refer to the VA/DOD CPG for the Management of Opioid Therapy for Chronic Pain.	Strong
8. For patients with acute low back pain or acute exacerbations of chronic low back pain, there is insufficient evidence to recommend for or against the use of **time-limited opioid therapy**. Given the significant risk and potential benefits of opioid therapy, patients should be evaluated individually, including consideration of psychosocial risks and alternative non-opioid treatments. Any opioid therapy should be kept to the shortest duration and lowest possible dose.	Not applicable
9. For patients with acute or chronic low back pain, there is insufficient evidence to recommend for or against the use of time-limited (less than 7 days) **acetaminophen therapy**.	Not applicable
10. For patients with chronic low back pain, the chronic use of **oral acetaminophen** is not recommended.	Strong

11. For the treatment of acute or chronic low back pain, including patients with both radicular and non-radicular low back pain, there is insufficient evidence to recommend for or against the use of **antiepileptics** including **gabapentin and pregabalin**	Not applicable
12. For the treatment of low back pain, there is insufficient evidence to recommend for or against the use of topical preparations	Not applicable

American Society of Clinical Oncology – Management of Chronic Pain in Survivors of Adult Cancers

Guidance for the management of chronic pain (pain persisting 3 months or more) in adult cancer survivors was published in 2020 by ASCO.[9] Methodology was clearly presented and a majority of authors had no conflicts of interest. A systematic review, ranging from 1996 to 2015, supported recommendations which were graded from weak to strong based on low, moderate or high quality of evidence. Pharmacological recommendations will be presented.

NSAIDs, acetaminophen and adjuvant analgesics (e.g., selected antidepressants [duloxetine] and selected antiepileptics [gabapentin and pregabalin]) with evidence of analgesic efficacy for neuropathic pain conditions or chronic widespread pain may be considered to relieve chronic pain and/or improve function (moderate recommendation: intermediate evidence quality).[9] Patients may be candidates for topical analgesics (e.g., NSAIDs, local anesthetics or compounded creams and gels containing baclofen, amitriptyline and ketamine) may be useful for chronic pain (moderate recommendation: intermediate evidence quality). Corticosteroids are not recommended for chronic pain relief alone (moderate recommendation: intermediate evidence quality).[9] Opioids may be considered in patients with chronic pain who do not respond to conservative management and continue to have pain or functional impairment (moderate recommendation: intermediate evidence quality).[9]

After review, 7 guidelines were excluded due to poor quality.[56–60]

New Formulations or Indications:

None identified

New FDA Safety Alerts:

Table 6. 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)
Ketorolac Nasal Spray[61]	Sprix®	1/2018	Indications and usage	Limitations of use: ketorolac is not for use in pediatric patients less than 2 years of age.
Celecoxib[62]	Celebrex®	6/2018	Warnings and Precautions	Celecoxib labeling was updated to include evidence that it was found to be noninferior to naproxen and ibuprofen for the risk of cardiovascular thrombotic risk (e.g. composite

				endpoint consisting of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke)
NSAID Class[63]	Not applicable	10/2020	Warnings and Precautions	The FDA is requiring changes to the prescribing information for prescription NSAIDs to describe the risk of kidney problems in unborn babies that result in low amniotic fluid.

Randomized Controlled Trials:

A total of 275 citations were manually reviewed from the initial literature search. After further review, 273 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Nissen, et al[64] (PRECISION) NI, DB, MC, RCT	Celecoxib 100 mg twice daily Vs. Ibuprofen 600 mg three times daily Vs. Naproxen 375 mg twice daily 20 month mean treatment duration	Adult patients with OA or RA who required NSAIDs and were increased CV risk N = 28,081	Composite outcome of CV death, nonfatal MI, or nonfatal stroke Noninferiority margin of HR 1.12 or lower and upper margin of 1.33 in ITT population and 1.40 or lower in per protocol population	<u>Composite Primary Outcome (per protocol population)</u> Celecoxib: 134 (1.7%) Naproxen: 144 (1.8%) Ibuprofen: 155 (1.9%) Celecoxib vs. Naproxen: HR 0.90 (95% CI, 0.71 to 1.15; p<0.001 for noninferiority) Celecoxib vs. Ibuprofen: HR 0.81 (95% CI, 0.65 to 1.02; p<0.001 for noninferiority) Ibuprofen vs. Naproxen: HR 1.12 (95%CI, 0.89 to 1.40; p=0.025 for noninferiority)
Chan, et al[65] DB, MC, RCT (CONDOR)	Celecoxib 200 mg twice daily Vs. Diclofenac 75 mg extended release	Adult patients with OA or RA at increased GI risk (e.g., gastroduodenal ulceration)	Clinically significant upper or lower GI event (e.g., gastroduodenal small-bowel or large-bowel hemorrhage, gastric-outlet obstruction, gastroduodenal small-bowel or large-bowel perforation,	<u>Primary endpoint (ITT population)</u> Celecoxib: 20 (0.9%) Diclofenac + omeprazole: 81 (3.8%) HR 4.3 (95% CI, 2.6 to 7.0; p<0.001)

	twice daily + omeprazole 20 mg once daily 6 month treatment duration	N= 4,484	clinically significant anemia of defined GI or presumed occult GI origin and acute GI hemorrhage of unknown origin.	

Abbreviations: CV – cardiovascular; DB – double-blind; GI – gastrointestinal; HR – hazard ratio; ITT – intention to treat; MC – multi-center; MI – myocardial infarction; NI – noniferiority; NSAIDs – non-steroidal anti-inflammatories; OA – osteoarthritis; RA – rheumatoid arthritis; RCT - randomized clinical trial.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL

diclofenac potassium	DICLOFENAC POTASSIUM	TABLET	PO	Y
diclofenac sodium	DICLOFENAC SODIUM	TABLET DR	PO	Y
etodolac	ETODOLAC	TABLET	PO	Y
flurbiprofen	ANSAID	TABLET	PO	Y
flurbiprofen	FLURBIPROFEN	TABLET	PO	Y
ibuprofen	IBUPROFEN	CAPSULE	PO	Y
ibuprofen	INFANTS IBUPROFEN	DROPS SUSP	PO	Y
ibuprofen	CHILDREN'S IBUPROFEN	ORAL SUSP	PO	Y
ibuprofen	IBUPROFEN	ORAL SUSP	PO	Y
ibuprofen	IBUPROFEN	TAB CHEW	PO	Y
ibuprofen	IBUPROFEN IB	TAB CHEW	PO	Y
ibuprofen	IBU	TABLET	PO	Y
ibuprofen	IBU-200	TABLET	PO	Y
ibuprofen	IBUPROFEN	TABLET	PO	Y
ibuprofen	IBUPROFEN IB	TABLET	PO	Y
ibuprofen	IBUPROHM	TABLET	PO	Y
ibuprofen	MOTRIN IB	TABLET	PO	Y
ibuprofen	PROVIL	TABLET	PO	Y
indomethacin	INDOMETHACIN	CAPSULE	PO	Y
ketoprofen	KETOPROFEN	CAPSULE	PO	Y
ketorolac tromethamine	KETOROLAC TROMETHAMINE	TABLET	PO	Y
meloxicam	MELOXICAM	TABLET	PO	Y
meloxicam	MOBIC	TABLET	PO	Y
nabumetone	NABUMETONE	TABLET	PO	Y
naproxen	NAPROXEN	TABLET	PO	Y
naproxen	EC-NAPROXEN	TABLET DR	PO	Y
naproxen	NAPROXEN	TABLET DR	PO	Y
naproxen sodium	ALL DAY PAIN RELIEF	TABLET	PO	Y
naproxen sodium	ALL DAY RELIEF	TABLET	PO	Y
naproxen sodium	NAPROXEN SODIUM	TABLET	PO	Y
naproxen sodium	NAPROXEN SODIUM DS	TABLET	PO	Y
oxaprozin	DAYPRO	TABLET	PO	Y
oxaprozin	OXAPROZIN	TABLET	PO	Y
salsalate	SALSALATE	TABLET	PO	Y
sulindac	SULINDAC	TABLET	PO	Y
celecoxib	CELEBREX	CAPSULE	PO	N
celecoxib	CELECOXIB	CAPSULE	PO	N
diclofenac potassium	ZIPSOR	CAPSULE	PO	N
diclofenac potassium	CAMBIA	POWD PACK	PO	N
diclofenac sodium	DICLOFENAC SODIUM ER	TAB ER 24H	PO	N

diclofenac sodium/misoprostol	ARTHROTEC 50	TAB IR DR	PO	N
diclofenac sodium/misoprostol	ARTHROTEC 75	TAB IR DR	PO	N
diclofenac sodium/misoprostol	DICLOFENAC SODIUM-MISOPROSTOL	TAB IR DR	PO	N
diclofenac submicronized	ZORVOLEX	CAPSULE	PO	N
diflunisal	DIFLUNISAL	TABLET	PO	N
etodolac	ETODOLAC	CAPSULE	PO	N
etodolac	ETODOLAC ER	TAB ER 24H	PO	N
fenoprofen calcium	FENOPROFEN CALCIUM	CAPSULE	PO	N
fenoprofen calcium	NALFON	CAPSULE	PO	N
fenoprofen calcium	FENOPROFEN CALCIUM	TABLET	PO	N
fenoprofen calcium	NALFON	TABLET	PO	N
ibuprofen/famotidine	DUEXIS	TABLET	PO	N
indomethacin	INDOMETHACIN ER	CAPSULE ER	PO	N
indomethacin	INDOCIN	ORAL SUSP	PO	N
indomethacin, submicronized	TIVORBEX	CAPSULE	PO	N
ketoprofen	KETOPROFEN	CAP24H PEL	PO	N
ketorolac tromethamine	KETOROLAC TROMETHAMINE	SPRAY	NS	N
ketorolac tromethamine	SPRIX	SPRAY	NS	N
meclofenamate sodium	MECLOFENAMATE SODIUM	CAPSULE	PO	N
mefenamic acid	MEFENAMIC ACID	CAPSULE	PO	N
meloxicam, submicronized	VIVLODEX	CAPSULE	PO	N
nabumetone	RELAFEN DS	TABLET	PO	N
naproxen	NAPROSYN	ORAL SUSP	PO	N
naproxen	NAPROXEN	ORAL SUSP	PO	N
naproxen sodium	NAPROXEN SODIUM	CAPSULE	PO	N
naproxen sodium	NAPRELAN	TBMP 24HR	PO	N
naproxen sodium	NAPROXEN SODIUM CR	TBMP 24HR	PO	N
naproxen sodium	NAPROXEN SODIUM ER	TBMP 24HR	PO	N
naproxen/esomeprazole mag	NAPROXEN-ESOMEPRAZOLE MAG	TAB IR DR	PO	N
naproxen/esomeprazole mag	VIMOVO	TAB IR DR	PO	N
piroxicam	FELDENE	CAPSULE	PO	N
piroxicam	PIROXICAM	CAPSULE	PO	N
tolmetin sodium	TOLMETIN SODIUM	CAPSULE	PO	N
tolmetin sodium	TOLMETIN SODIUM	TABLET	PO	N

Appendix 2: Abstracts of Comparative Clinical Trials

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E Nissen , Neville D Yeomans , Daniel H Solomon , Thomas F Lüscher , Peter Libby , M Elaine Husni , David Y Graham , Jeffrey S Borer , Lisa M Wisniewski , Katherine E Wolski , Qiuqing Wang , Venu Menon , Frank Ruschitzka , Michael Gaffney , Bruce Beckerman , Manuela F Berger , Weihang Bao , A Michael Lincoff , PRECISION Trial Investigators

Background: The cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal antiinflammatory drugs (NSAIDs), remains uncertain.
Methods: Patients who required NSAIDs for osteoarthritis or rheumatoid arthritis and were at increased cardiovascular risk were randomly assigned to receive celecoxib, ibuprofen, or naproxen. The goal of the trial was to assess the noninferiority of celecoxib with regard to the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke. Noninferiority required a hazard ratio of 1.12 or lower, as well as an upper 97.5% confidence limit of 1.33 or lower in the intention-to-treat population and of 1.40 or lower in the on-treatment population. Gastrointestinal and renal outcomes were also adjudicated.
Results: A total of 24,081 patients were randomly assigned to the celecoxib group (mean [±SD] daily dose, 209±37 mg), the naproxen group (852±103 mg), or the ibuprofen group (2045±246 mg) for a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months. During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (hazard ratio for celecoxib vs. naproxen, 0.93; 95% confidence interval [CI], 0.76 to 1.13; hazard ratio for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%) (hazard ratio for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15; hazard ratio for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02; P<0.001 for noninferiority in both comparisons). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib than with naproxen (P=0.19).
Conclusions: At moderate doses, celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety. (Funded by Pfizer; ClinicalTrials.gov number, NCT00346216 .)

Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial

Francis K L Chan , Angel Lanas, James Scheiman, Manuela F Berger, Ha Nguyen, Jay L Goldstein

Abstract
Background: Cyclo-oxygenase (COX)-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) and non-selective NSAIDs plus a proton-pump inhibitor (PPI) have similar upper gastrointestinal outcomes, but risk of clinical outcomes across the entire gastrointestinal tract might be lower with selective drugs than with non-selective drugs. We aimed to compare risk of gastrointestinal events associated with celecoxib versus diclofenac slow release plus omeprazole.
Methods: We undertook a 6-month, double-blind, randomised trial in patients with osteoarthritis or rheumatoid arthritis at increased gastrointestinal risk at 196 centres in 32 countries or territories. Patients tested negative for Helicobacter pylori and were aged 60 years and older or 18 years and older with previous gastroduodenal ulceration. We used a computer-generated randomisation schedule to assign patients in a 1:1 ratio to receive celecoxib 200 mg twice a day or diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day. Patients and investigators were masked to treatment allocation. The primary endpoint was a composite of clinically significant upper or lower gastrointestinal events adjudicated by an independent committee. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00141102.

Findings: 4484 patients were randomly allocated to treatment (2238 celecoxib; 2246 diclofenac plus omeprazole) and were included in intention-to-treat analyses. 20 (0.9%) patients receiving celecoxib and 81 (3.8%) receiving diclofenac plus omeprazole met criteria for the primary endpoint (hazard ratio 4.3, 95% CI 2.6-7.0; p<0.0001). 114 (6%) patients taking celecoxib versus 167 (8%) taking diclofenac plus omeprazole withdrew early because of gastrointestinal adverse events (p=0.0006).
Interpretation: Risk of clinical outcomes throughout the gastrointestinal tract was lower in patients treated with a COX-2-selective NSAID than in those receiving a non-selective NSAID plus a PPI. These findings should encourage review of approaches to reduce risk of NSAID treatment.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 03, 2020
Search Strategy:

#	Searches	Results
1	diclofenac.mp. or Diclofenac/	13436
2	etodolac.mp. or Etodolac/	699
3	flurbiprofen.mp. or Flurbiprofen/	2704
4	ibuprofen.mp. or Ibuprofen/	15293
5	indomethacin.mp. or Indomethacin/	42850
6	ketoprofen.mp. or Ketoprofen/	4376
7	meloxicam.mp. or Meloxicam/	2305
8	nabumetone.mp. or Nabumetone/	493
9	Naproxen/ or naproxen.mp.	7007
10	oxaprozin.mp. or Oxaprozin/	163
11	salsalate.mp.	182
12	sulindac.mp. or Sulindac/	2077
13	celecoxib.mp. or Celecoxib/	7075
14	diflunisal.mp. or Diflunisal/	814
15	fenoprofen.mp. or Fenoprofen/	496
16	meclofenamate.mp. or Meclofenamic Acid/	1318

17	mefenamic acid.mp. or Mefenamic Acid/	1701
18	piroxicam.mp. or Piroxicam/	3987
19	tolmetin.mp. or Tolmetin/	1451
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	91620
21	limit 20 to (english language and humans)	37162
22	limit 21 to yr="2016 -Current"	4569
23	limit 22 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	275

Appendix 4: Key Inclusion Criteria

Population	Patients with pain and/or inflammation
Intervention	Non-steroidal anti-inflammatories
Comparator	Placebo or active treatment comparison
Outcomes	Pain relief, improvement in function, improvement in disability
Timing	Onset of pain
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Analgesics, Non-Steroidal Anti-Inflammatory Drugs

Goal(s):

- To ensure that non-preferred NSAIDs are used for conditions funded by the OHP.
- Restrict ketorolac to short-term use (5-day supply every 60 days) per the FDA black boxed warning.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred NSAIDs.
- Ketorolac: Maximum of one claim per 60 days, with a maximum 20 tablets/5-day supply or 126 mg/day for nasal spray (maximum 5-day combined duration of treatment every 60 days).

Preferred Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by the Oregon Health Plan?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this a request for ketorolac, new or continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #4.	**No:** Go to #5
4. Is request for more than a 5-day supply of ketorolac within 60 days (200 mg total over 5 days for tablets, 630 mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based and reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 12 months.

P&T Review: *2/21 (KS), 3/16 (MH); 11/14; 9/13; 2/12; 9/09; 2/06*
Implementation: *1/1/15, 1/1/14, 5/14/12, 1/1/10*