Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 27, 2017 1:00 - 5:00 PM
Barbara Roberts Human Services Building, HSB 137 A-D
500 Summer St. NE
Salem, OR 97301

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 as required by 414.325(9).

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)
	II. DUR NEW BUSINESS	
1:10 PM	A. CMS Annual Report	D. Weston (OHA)
1:20 PM	B. Prioritization of PA Criteria Implementation	R. Citron (OSU)
	1. PA Criteria Awaiting Implementation	
	2. DXC Bandwidth	
	3. Discussion of PA Implementation Prioritization	
	III. PREFERRED DRUG LIST NEW BUSINESS	
1:40 PM	A. Biologics Class Update	D. Moretz (OSU)
	1. Class Update/Prior Authorization Criteria	S. Servid (OSU)
	2. Siliq® (brodalumab) New Drug Evaluation	
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	
2:20 PM	B. Antidiabetic Agents (non-insulin products)	K. Sentena (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

2:50 PM	C. Spinraza® (nusinersen) 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:05 PM	BREAK	
3:15 PM	D. Emflaza® (deflazacort) 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:30 PM	E. Exondys 51® (eteplirsen) 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:45 PM	F. Literature Scans 1. Pancreatic Enzymes 2. Topical Corticosteroids 3. Antiplatelets 4. Topical Antipsoriatics 5. Newer Antiemetics 6. Public Comment 7. Discussion of Clinical Recommendations to OHA	 D. Engen (OSU) M. Herink (OSU) K. Sentena (OSU)
4:15 PM	G. Abbreviated Drug Reviews 1. Trulance® (plecanatide) 2. Symproic® (naldemedine) 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
4:25 PM	IV. EXECUTIVE SESSION	
4:50 PM	V. RECONVENE for PUBLIC RECOMMENDATIONS	
5:00 PM	VI. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 25, 2017, 1:00-5:00 PM
Human Services Building
Salem, OR 97301

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 as required by 414.325(9).

Members Present: Kelley Burnett, DO; Rich Clark, MD, MPH; Walter Hardin, D.O., MBA; Tracy Klein, PhD, FNP; Phil Levine, PhD; Caryn Mickelson, PharmD; William Origer, MD; James Slater, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Stacy Ramirez, PharmD; Dave Pass, MD

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Dee Weston; Sarah Servid, PharmD; Deanna Moretz, PharmD, BCPS; Lindsay Newton; Megan Herink, PharmD, BCPS; Melissa Smith, PharmD; Kim Vo, PharmD; Dave Engen, PharmD; Kathy Sentena, PharmD; Kim Wentz, MD

Staff Present by Phone: Dean Haxby, PharmD

Audience: *Arti Baig, Pfizer; Jim Graves, Bristol-Meyers Squibb; Rick Frees, Vertex; Venus Holder, Lilly; Cathy Gross, Purdue; Jen Lee, AllCare Health; Keri Smith, UiiU; Chris Conner, Bristol-Meyers Squibb; Bobbi Jo Drum, Bristol-Meyers Squibb; Georgette Dawilewski, Indivior; Tracy, Vertex; Tim McFerron, Alkermes; Jennifer Shidler, SanofiGenazne; Patrick Nave, Purdue; Robin Traver, Umpqua Health Alliance; *Mary Kemtius, Norvartis; *Lowen Sandt, Caring Ambassadors; Lisa Boyle, WVP Health Authority; Joe Schreck, Allergan; *Kim Lambmeier, Sunovion; *Lyle Laird, Sunovion; Jeana Colabianchi, Sunovion; Margaret Olman, AbbVie; Cheryl Fletcher, AbbVie; Karen Jackson, Trividia; David Barhoum, Genetech; John Bullard, Amgen; Sohrob Yarari, Pacific University; *Shelley Bailey, Central Drugs; Amy Bannon, Pfizer; *Mae Kwong, Janssen

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:00 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.
C. Approval of agenda and March minutes presented by Mr. Citron. (pages 5 - 8)

ACTION: Motion to approve, 2nd, All in Favor.

II. DUR OLD BUSINESS

A. Hepatitis C Policy Update (pages 9-18)
Mr. Citron reviewed the MOU the OHA has entered into with the OLC which required modifications to the DAA PA criteria to become effective on 6/1/2017
B. Updated DAA Criteria
Mr. Citron presented the updated PA criteria reflecting the required changes and the Committee recommended amending the language in question #14, adding a link to the HERC coverage guidance in questions #7 & 8.
C. Public Comment
D. Discussion of Clinical Recommendations to OHA

ACTION: Motion to approve recommended edits to questions #7, 8 and 14. 2nd. All in favor. Approved. While understanding the OHA is bound by the MOU the Committee made a Motion to remove the guidance regarding handling of fibrosis test results indicating a range is n questions #7 and 8 and to instead address through their contracts and guidance to the CCOs. 2nd. Majority in favor. Approved.

III. DUR ACTIVITIES

A. Quarterly Utilization Reports
B. ProDUR Report
C. RetroDUR Report
D. Oregon State Drug Reviews
    a. Non-Analgesics for Pain Management.
    b. Management of Opioid Use Disorder.

IV. DUR NEW BUSINESS

A. HERC Novel Treatments (pages 34 - 37)
Mr. Citron reviewed the HERC's Statement of Intent in regards to the review of Novel Treatments and presented the proposed High Cost and Marginal Benefit (HCMB) Therapies Policy:

1. Approve proposed P&T policy.
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

ACTION: Motion to approve after changing "elect" to "vote" in item #3 in the proposed policy, 2nd. All in favor. Approved.

B. Pediatric Antipsychotic Metabolic Monitoring (pages 38 - 60)
Dr. Servid presented the evaluation and the following recommendation:

1. Approve discontinuation of RetroDUR fax initiative

ACTION: Motion to approve, 2nd. All in favor. Approved.

C. Non-Vitamin K Antagonists Oral Anticoagulants (NOACs) (pages 61 - 90)
Dr. Vo and Dr. Sentena presented the scan and policy evaluation with the following recommendations:

1. No further research is needed and the evidence does not support a clinical prior authorization on NOACs at this time.
2. Continue to monitor for appropriate use
3. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

D. Proton Pump Inhibitors (pages 91 – 119)
Dr. Sentena and Dr. Smith presented the scan and policy evaluation with the following recommendations:

1. No further research is needed at this time.
2. Add dexlansoprazole SoluTabs and update PA criteria.
3. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

V. PREFERRED DRUG LIST NEW BUSINESS

A. Ophthalmic VEGF Inhibitor Class Update (pages 120 - 142)
Dr. Servid presented the class update and following recommendations:

1. Approve proposed PA criteria for non-preferred drugs and apply to both pharmacy and physician administered claims.
2. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

B. Tetracycline Antibiotics Class Update (pages 143 - 151)
Dr. Herink presented the class update and following recommendations:

1. Change quantity limit to allow two 14 day supplies in a 3 month timeframe.
2. Remove the quantity limit and PDL status for demeclocycline
3. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

C. Literature Scans (pages 152 - 169)
Dr. Moretz, Dr. Sentena, Dr. Herink and Dr. Servid presented the literature scans and following recommendations:

1. ACEIs, ARBs, DRIs and Entresto (sacubitril/valsartan) (pages 152-169)
    a. No further research is needed at this time
    b. Maintain current PA criteria
    c. Evaluate comparative costs in executive session
2. Anaphylaxis Rescue Agents Scan (pages 170-174)
    a. No further research is needed at this time
    b. Evaluate comparative costs in executive session
3. Antianginal Agents (pages 175-183)
    a. Maintain sublingual powder nitroglycerin (GONITRO™) as non-preferred on the PMPDP
    b. No further research is needed at this time
    c. Evaluate comparative costs in executive session
4. Otic Antiabiotics (pages 184-190)
    a. No further research is needed at this time
    b. Continue to have at least on preferred product for treatment of acute otitis media in patients with tympanostomy tubes and at least one ototopical aminoglycoside antibiotic as an option for otitis externa
    c. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

D. Abbreviated Drug Reviews (pages 191 - 198)
Dr. Servid presented the class update and following recommendation:

1. Intrarosa® (pages 191-192)
    a. Require PA to restrict use to OHP-funded conditions.
2. Eurcrisa® (page 193)
    a. Require PA to restrict use to OHP-funded conditions.
3. Amulez® (page 194)
    a. Require PA to restrict use to OHP-funded conditions.
4. Levulan® (page 195-196)
    a. Require PA to restrict use to OHP-funded conditions.
5. Rhofade® (page 197)
    a. Add drug to list of drugs for excluded conditions
6. Belviq® (page 198)
    a. Add drug to list of drugs for excluded conditions

ACTION: Motion to approve, 2nd. All in favor. Approved.

VI. EXECUTIVE SESSION

VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Non-Vitamin K Antagonists Oral Anticoagulants (NOACs) (pages 61 - 90)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

B. Proton Pump Inhibitors (pages 91 – 119)
*__ACTION:__ Make Ranitidine 150mg tablets, Ranitidine 300mg tablets, Famotidine 20mg tablets, and Famotidine 40mg tablets preferred.
Motion, 2nd, All in Favor. Approved.

C. Ophthalmic VEGF Inhibitor Class Update (pages 120 - 142)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

D. Tetracycline Antibiotics Class Update (pages 143 - 151)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

E. ACEIs, ARBs, DRIs and Entresto (sacubitril/valsartan) (pages 152-169)
*__ACTION:__ Add irbesartan and valsartan to the PMPDP as preferred.
Motion, 2nd, All in Favor. Approved.

F. Anaphylaxis Rescue Agents Scan (pages 170-174)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

G. Antianginal Agents (pages 175-183)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

H. Otic Antiabiotics (pages 184-190)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

VIII. ADJOURN

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Biologics for Autoimmune Conditions

Date of Review: July 2017
Dates of Prior Reviews: November 2016 (DERP summary) and September 2014

End Date of Literature Search: 05/01/2017

Generic Name: Brodalumab

Brand Name (Manufacturer): Siliq® (Valeant Pharmaceuticals)
Dossier Received: Yes

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

Purpose for Class Update:
To define place in therapy for 1 new biologic response modifier recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of moderate to severe plaque psoriasis. In addition, new comparative evidence for existing biologics (targeted immune modulators) will be reviewed.

Research Questions:

- Is there new comparative evidence that biologic response modifiers differ in effectiveness for alleviating symptoms and stabilizing disease in patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) , ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease , ulcerative colitis, or plaque psoriasis (PsO)?
- Is there any new comparative evidence the biologic response modifiers differ in harms?
- Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?
- Is brodalumab more effective than currently available agents for the treatment of moderate to severe plaque psoriasis?
- Is brodalumab safer than currently available agents for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- For the treatment of RA, four systematic reviews provide moderate quality evidence to support the efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib in improving disease activity and function compared to conventional disease modifying antirheumatic drug (DMARD) therapy.[1-4] In head-to-head trials of biologic therapy combined with a DMARD versus adalimumab monotherapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, American College of Rheumatology (ACR) response, and improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI).[5]
- Compared with placebo, there is high quality evidence that patients on a tumor necrosis factor (TNF) inhibitor are 3 to 4 times more likely to achieve an improvement in ankylosing spondylitis (AS) clinical symptoms as measured by Assessment of Spondyloarthritis (ASAS) 40 response within 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95%

CI 2.80 to 5.74, with a 25% to 40% absolute difference between treatment and placebo groups.[6] There is a lack of head to head trials to define superiority of one agent over another for the treatment of AS.

- In 6 direct comparative trials evaluating treatment of adults with PsO ustekinumab, secukinumab, and ixekizumab were superior to etanercept for disease severity, measured by the Psoriasis Area Severity Index (PASI) 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100. Refer to Table 6 for specific results of the six different head-to-head trials. One-year follow-up of pivotal trials demonstrate that etanercept, ustekinumab, secukinumab, and brodalumab have comparable safety profiles when used for the treatment of psoriasis.[7] There is limited comparative data in pediatric patients.
- There is moderate to high quality evidence of no increase in the risks of breast cancer, lymphoma, or non-melanoma skin cancer (NMSC) with TNF inhibitors compared to placebo in RA studies. There is insufficient evidence on total malignancy risk. In IBD, PsA, and PsO patients, TNF inhibitors were not associated with elevated cancer risk compared to control groups.[8]
- Evidence is inconclusive for withdrawals due to adverse events, rates of cancer occurrence, and rates of serious adverse events with biological response modifiers compared to conventional therapy.[1-4]
- There is moderate quality evidence that treatment with brodalumab 210 mg every 2 weeks results in a statistically significant improvement in symptoms compared to placebo (as evaluated by PASI75) in patients with moderate to severe PsO (absolute risk reduction [ARR] of 79 to 81%, number-needed-to-treat [NNT] 2). Evaluation of symptoms using a static physician's global assessment (sPGA) score of 0 or 1 corresponding to clear or almost clear skin, resulted in similar improvements.[9]
- There is moderate quality evidence that compared to ustekinumab, more patients with PsO treated with brodalumab achieved complete disease clearance (PASI100 or sPGA of 0) at 12 weeks (37-44% vs. 19-22%; ARR 18-22%, NNT 5-6). The proportion of PsO patients with 75% improvement in PASI score was also improved with brodalumab treatment compared to ustekinumab (low quality evidence).
- There is insufficient evidence to determine differences in long-term efficacy, remission rates, health-related quality of life, or functional improvement with brodalumab compared to other treatments for moderate to severe PsO.
- There is insufficient evidence to determine long-term safety of brodalumab or differences in safety compared to currently available treatments for moderate to severe plaque psoriasis. During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides. In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Furthermore, due to significant safety concerns associated with long-term treatment, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.[10]
- There is insufficient evidence to determine differences in efficacy or safety of brodalumab compared to other biologic agents for specific demographics or populations including subgroups based on age, gender, ethnicity, prior treatment or concurrent psoriasis treatments, disease duration or severity, or concomitant psoriatic arthritis.
- There is no evidence regarding the efficacy or safety of brodalumab for conditions other than moderate to severe plaque psoriasis. It has also been evaluated in clinical trials for the treatment of psoriatic arthritis and axial spondyloarthritis though trials were discontinued with due to safety concerns associated with brodalumab use.[11]

Recommendations:

- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Decrease age for abatacept to ≥ 2 years old for juvenile idiopathic arthritis
    - Decrease age for etanercept to ≥ 4 years old for plaque psoriasis
    - Add Crohn's Disease indication for ustekinumab for patients ≥ 18 years

- Remove alefacept from PA criteria as it is no longer marketed in the United States.
- Require trial and failure of adalimumab or enteracept for arthritic or psoriatic conditions or ankylosing spondylitis before advancing to another biologic agent. Require trial and failure of adalimumab before advancing to another biologic for Crohn's Disease.
- Because brodalumab is associated with significant safety concerns including suicidal ideation and behavior, add brodalumab as a non-preferred drug to the PDL. Modify PA criteria to include brodalumab for use in moderate to severe plaque psoriasis.
- Evaluate comparative costs in executive session.

Previous Conclusions:

Efficacy Comparisons

- Low quality evidence suggests that all biologic immunosuppressant treatments approved by the FDA for rheumatoid arthritis have similar efficacy. Specific comparisons between biologics are limited to single head-to-head studies.
- Evidence for differences between biologic treatments for juvenile idiopathic arthritis is insufficient. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ankylosing spondylitis is insufficient. No head-to-head trials were identified.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for biologic treatments for psoriatic arthritis. Evidence from a single head-to-head clinical trial demonstrated equal efficacy between adalimumab, etanercept and infliximab in adults. No head-to-head trials were in children.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for FDA-approved biologic treatments for Crohn's disease. Evidence for differences in efficacy between biologic treatments is limited to low quality evidence based on one open-labeled study which did not find a difference between adalimumab and infliximab for clinical recurrence rates following curative ileocolic resection. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ulcerative colitis is insufficient. No head-to-head trials were identified.

Safety Comparisons

- Most comparative evidence available for harms outcomes is for the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab. There is moderate quality evidence that infliximab is associated with higher risk for serious infections and discontinuation of therapy due to adverse events than abatacept, adalimumab and etanercept. Specifically, risk for tuberculosis may be higher with adalimumab or infliximab compared to etanercept based on low quality evidence. Low quality evidence does not suggest any differences for risk of herpes zoster between TNF inhibitors.
- Low quality evidence suggests infliximab and adalimumab may be associated with more injection site or infusion reactions than abatacept. Low quality evidence also suggests etanercept may be associated with higher risk of injection site reactions than adalimumab, secukinumab and ustekinumab.
- Low quality evidence suggests no differences in risk for cancer between biologic treatments.
- There is high quality evidence that the combination of 2 biologic agents is associated with higher risk for serious adverse events, discontinuation due to adverse events, and serious infections without additional therapeutic benefit.
- There is insufficient evidence in children to make conclusions on differences in harms between biologic treatments.
- There is insufficient evidence to determine if differences in efficacy or harms exist between biologic treatments for the pre-specified subgroup populations.

Previous Recommendations:

- Modify prior authorization criteria to include new FDA approved indications and new medications.
- Evaluate comparative costs of newly approved agents in executive session; Make golimumab non-preferred.

Background:

Biological response modifiers also classified as targeted immune modulators, have proven to be safe and efficacious in treating arthritis, psoriasis, ankylosing spondylitis, and inflammatory bowel diseases. The exact etiology of these autoimmune conditions is unclear but appears to involve upregulation of multiple inflammatory factors. Approaches to treating rheumatic diseases with biologic agents include interference with cytokine function, inhibition of T-cell activation, or depletion of B cells. **Table 1** outlines the approved indications for each of the biologic agents. **Table 2** presents the mechanism of action and dosing strategies for the biological response modifiers. The outcome measures used to assess response to therapy are summarized in **Table 3**. Each indication for which biologics have proven efficacy will be briefly summarized below.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity. Other tissues and organs, including the heart, kidney, and lungs, may also be affected. The 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 and interleukins. In 2005, the prevalence of RA in the U.S. was estimated to be 0.6% of the adult population.[12] The diagnosis of RA increases after the fourth decade of life and is 3 times more likely in women than men.[13] According to the ACR, first line treatment of early RA is an oral nonbiologic DMARD such as methotrexate (MTX), leflunomide, sulfasalazine, or hydroxychloroquine.[14] Monotherapy with MTX is the preferred therapy. This recommendation is based on low quality evidence, but had strong support from the ACR panel due to ease of patient access and relatively low cost of therapy. For patients with established RA with continued disease activity despite DMARD therapy, biologics are recommended to improve function and control RA symptoms. The TNF inhibitors adalimumab, certolizumab, etanercept, golimumab, and infliximab are approved by FDA to manage RA. Other injectable biologics approved to manage RA are abatacept, anakinra, rituximab and tocilizumab. One oral agent, tofacitinib, a janus kinase inhibitor, was approved by FDA for RA in 2012. There is a lack of head to head comparative effectiveness trials in the class and no one agent has demonstrated superiority over another.[15]

Primary endpoints used in RA clinical trials are the ACR response, the HAQ-DI, and the Disease Activity Score 28 (DAS-28). The ACR response is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity. Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts in at least 3 of the domains. ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in at least 3 domains.[15] ACR 50 and 70 are considered more clinically significant than ACR 20. The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[15] The DAS-28 is another index of disease activity (similar to the ACR response). A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS-28 score of 2.6 is considered to correspond to remission.[15]

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) occurs in children under the age of 16 years who present with joint inflammation of unknown etiology lasting longer than 6 weeks.[16] In 2001, the International League of Associations of Rheumatology (ILAR) proposed classification criteria for chronic childhood arthritis to enhance diagnosis and optimize treatment.[17] The umbrella term "juvenile idiopathic arthritis" was chosen and the disease was subdivided into 7 categories according to

clinical presentation, disease course, and treatment response. The 7 categories are: systemic arthritis, oligoarthritis, rheumatoid factor (RF) negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. The oligoarticular subtype occurs in 50-60% of cases.[18] JIA is the most common pediatric rheumatic disease and occurs in 16-150 cases per 100,000 children in developed countries.[16] The goals of treatment for JIA include: suppression of inflammation, achievement of remission, relief of pain, maintenance of function and minimizing toxicity.[19] Nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in treating pain associated with mild disease. Intra-articular steroid injections are used in patients with oligoarticular JIA. Disease-modifying agents such as MTX have demonstrated efficacy and safety; however some patients do not respond to DMARD therapy and progress to treatment with biologic agents. Biologic agents are selected according to the presenting symptoms and JIA stratification. Effective therapies include TNF inhibitors (adalimumab, etanercept and infliximab) and abatacept (a T-cell inhibitor). Interleukin inhibitors such as canakinumab and tocilizumab are two additional agents used to manage the systemic form of JIA.[20]

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine. Bone inflammation results in formation of entheses, or attachment points between tendon, ligament, and bone.[21] Cytokine production released during inflammation affects osteoclast and osteoblast activity which can lead to paradoxical systemic bone loss, despite new bone formation which causes fusion of joints or the spine.[22] Prevalence estimates in the US are between 0.9 to 1.4% of the adult population.[23] The male: female ratio is around 5:1, with a peak age of onset between 15 to 35 years.[21] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom; low back pain for ≥ 3 months, limited lumbar spine motion, or decreased chest expansion for age and sex.[24] Patients who have chronic pain and other features suggestive of AS without radiologic changes are classified as having nonradiographic axial spondyloarthritis (SpA).[25] Organ involvement can result in uveitis, psoriasis, and inflammatory bowel disease (IBD). Guidelines for management of AS were updated in 2010 by the Assessments in Ankylosing Spondylitis International Society (ASA) and the European League against Rheumatism (EULAR). NSAIDs and exercise are recommended as first line therapies to alleviate pain and stiffness.[26] TNF inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[26] Five TNF inhibitors including infliximab, etanercept, adalimumab, certolizumab, and subcutaneous golimumab are proven to provide sustained improvement in disease activity and patient functioning as assessed by the Bath ankylosing spondylitis disease activity index (BASDI) and functional index (BASFI) scores.[23] The anti–interleukin monoclonal antibody, secukinumab, also has proven efficacy in treating AS.[27] There is no evidence for the efficacy of systemic glucocorticoids or DMARDs in the treatment of AS, although sulfasalazine may be considered for patients with peripheral arthritis.[26]

Plaque Psoriasis

Plaque psoriasis (PsO) is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[28,29] Plaque psoriasis affects men and women equally, with the onset peaking between the ages 30 to 39 and 50 to 69 years, and affects about 2% of the U.S. population.[29] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[30] People with psoriasis, especially those with severe disease, are also at increased risk of cardiovascular disease, diabetes, and depression.[28] The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, smoking, infections, drugs, obesity, stress, and alcohol consumption.[31] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 10% of the body surface area and has little to no impact on quality of life or function. Mild psoriasis is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[32] Per NICE guidance, topical medications including corticosteriods and vitamin D analogs, such as calcipotriene, or coal tar are first line agents for PsO.[33] Phototherapy is an option for moderate to severe PsO that has not responded to topical therapy. Systemic nonbiologic treatments are recommended for moderate to severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics are added for moderate to severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include adalimumab, etanercept, infliximab, ustekinumab, and secukinumab. A 2015 systematic review

and meta-analysis evaluating injectable biologic treatments for least 24 weeks found evidence to support infliximab, secukinumab, and ustekinumab as the most effective long-term PsO therapies.[34] Two newer injectable therapies approved to manage PsO, ixekizumab and brodalumab, were not included in the systematic review completed in 2015. An oral phosphodiesterase 4 (PDE4) inhibitor, apremilast, is also approved for treatment of moderate to severe PSO.

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the psoriasis area and severity index (PASI), the static physician's global assessment scale (sPGA), or the psoriasis symptom inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[35] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head and extremities, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[35,36] It does not take into account symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[35] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[36] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, improvements of 100%, indicating complete disease clearance, are considered more clinically significant.[37] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5). Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[37] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed including itch, redness, scaling, burning, stinging, cracking, flaking and pain.[37] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[37] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy.[38]

Psoriatic Arthritis

Psoriatic arthritis (PsA) is classified as a spondyloarthropathy and characterized by synovitis, enthesitis, dactylitis as well as skin and nail psoriasis.[39] PsA can develop at any time including childhood, but for most patients, it appears between the ages of 30 and 50 years.[40] PsA affects men and women equally. PsA symptoms include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons. Common locations include the insertion sites of the plantar fascia, the Achilles' tendons, and ligamentous attachments to the ribs, spine, and pelvis. Dactylitis, or "sausage digit," is a combination of enthesitis of the tendons and ligaments and synovitis involving a whole digit.[40] The prevalence of PsA in the general population of the United States is relatively rare and ranges from 6 to 25 cases per 10,000 people.[41] Approximately 30% of patients with psoriasis with have symptoms of PsA.[41] PsA has been sub-classified as mild, moderate and severe depending on response to therapy and patient functional status. Initially, management of PsA was extrapolated from experiences in managing RA.[42] The European League against Rheumatism (EULAR) developed PsA management recommendations in 2011 to improve management of this disease.[43] First line treatment recommendations include NSAID therapy to alleviate joint pain, but it is recognized that NSAIDs cannot improve skin lesions. DMARD therapy (MTX, sulfasalazine or leflunomide) should be initiated in patients with active disease (one or more inflamed joints) and poor prognosis (> 5 actively inflamed joints).[43] If DMARD therapy is not effective, TNF inhibitors (adalimumab, etanercept, subcutaneous golimumab or infliximab) should be added to improve skin and joint symptoms, as well as to prevent radiographic damage.[43] More recent guidelines advocate for the use of secukinumab, ustekinumab, and apremilast for PsA that does not respond to TNF inhibitors.[44,45]

Crohn's Disease

Crohn's disease (CD), is characterized by transmural inflammation of any part of the gastrointestinal tract, but most often affects the small bowel and colon.[46] CD is progressive and markedly impairs patient quality of life due to its associated symptoms such as gastrointestinal bleeding, nausea, vomiting, diarrhea,

abdominal cramps, weight loss and fever. The prevalence of CD in the U.S. is estimated as 50 per 100,000 persons.[47] CD is incurable; it begins in young people between the ages of 10 and 30 years and continues throughout life. The anatomic evolution of CD has been determined from studies of postoperative recurrence; CD begins with aphtous ulcers that develop into strictures or fistulas.[47] Among patients with CD, intestinal surgery is required for as many as 80% and a permanent stoma required in more than 10%.[46] Approved biologics to manage CD are infliximab, adalimumab, natalizumab, and vedolizumab. AHRQ clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy.[48] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission). Some experts believe that patients have better long-term outcomes taking immunomodulators and biologics early ("top-down therapy"), as opposed to taking them after prolonged steroid use ("step-up therapy").[48] There is controversy over which method is more effective and currently the step-up strategy remains standard of care.[48] The order of medications from top down is biologics, non-biologic immunomodulators, corticosteroids, and aminosalicylates.[48] A recent randomized controlled trial compared conventional step therapy to early combined immunosuppression therapy with a TNF inhibitor (top-down therapy) and found no significant benefit in remission rates compared to conventional therapy with a lower rate of major adverse outcomes.[49] The American Gastroenterological Association (AGA) strongly recommends induction with an anti-TNF drug in patients who have moderately severe CD despite standard therapies, and to maintain corticosteroid or TNF inhibitor induced remission.[50] NICE guidelines recommend TNF inhibitors for induction, but only after failure of conventional therapy with corticosteroids, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[51]

Ulcerative Colitis

Ulcerative colitis (UC) is a relapsing and remitting form of IBD, with inflammation typically restricted to the colon and rectum.[52] Symptoms include bloody diarrhea with or without mucus, abdominal pain, weight loss, fatigue, rectal urgency and tenesmus.[53] Unlike CD, UC is limited to the colon and does not usually present with fistulas or strictures. The onset of symptoms and diagnosis of UC usually occurs in young to middle aged adults. The peak age of onset is between 15 and 30 years of age.[54] The prevalence in the U.S. is approximately 100-200 cases per 100,000 people.[54] Smoking is protective for UC but it is a risk factor for CD. In patients with UC, the lesions usually remain superficial and extend proximally. Colectomy is required for 10%–30% of patients.[55] Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition. The lifetime risk of a severe exacerbation requiring hospitalization is between 15% and 25%.[55] Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%.[56] Treatment for UC aims to relieve symptoms during a flare-up and then to maintain remission. Infliximab is recommended by the NICE guidelines as an induction option for acute exacerbations of severely active UC only in patients in whom cyclosporine is contraindicated or clinically inappropriate.[57] The American College of Gastroenterology (ACG) and the NICE Guidelines recommend the use of biologic agents (infliximab, adalimumab, vedolizumab, golimumab) for treating moderately to severely active UC in adults whose disease has responded inadequately to, or have intolerance or contraindications to, to conventional therapy including corticosteroids and mercaptopurine or azathioprine.[52,58,59] Continuation of these agents is only recommended if there is clear evidence of response.[51,52]

Fee-for-Service Utilization January 1, 2017 to March 31, 2017

In the first quarter of 2017 there were approximately 125 pharmacy claims for biologic agents in fee-for-service (FFS) population. Seventy-five percent of the claims were for the preferred agents; either etanercept or adalimumab. There were no pharmacy claims for anakinra, infliximab, or vedolizumab. There were 1-2 claims each for the following nonpreferred agents: abatacept, apremilast, certolizumab, tocilizumab, ustekinumab, tofacitinib, golimumab, and secukinumab. All prior authorization requests were approved. Most of the claims (75%) for biologic agents that were not paid by FFS were subsequently paid by coordinated care organizations (CCOs). No prior authorization request was submitted for 8% of claims that were not paid. Other reasons claims FFS did not pay the claims were because the member lost eligibility or another insurance paid the claim.

Table 1. Approved Indications for Biologic Immunosuppressants[60,61]

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Hidradenitis Suppurativa	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infectious)	Other
Abatacept (ORENCIA)				≥2 yo		≥18 yo	≥18 yo			
Adalimumab (HUMIRA)	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Anakinra (KINERET)							≥18 yo			NOMID
Apremilast (OTEZLA)					≥18 yo	≥18 yo				
Brodalumab (SILIQ)					≥18 yo					
Canakinumab (ILARIS)				≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPs ≥ 4 yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept (ENBREL)	≥18 yo			≥2 yo	≥4 yo	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo					≥18 yo	≥18 yo (SIMPONI ARIA is only FDA approved for RA)	≥18 yo		
Infliximab (REMICADE)	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Infliximab-dyyb (INFLECTRA)	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥18 yo		
Ixekizumab (TALTZ)					≥18 yo					
Natalizumab (TYSABRI)		≥18 yo								MS ≥18 yo
Rituximab (RITUXAN)							≥18 yo			CLL ≥18 yo NHL ≥18 yo

										GPA ≥18 yo
Secukinumab (COSENTYX)	≥18 yo				≥18 yo	≥18 yo				
Sarilumab (KEVZARA)							≥18 yo			
Tocilizumab (ACTEMRA)				≥2 yo			≥18 yo			
Tofacitinib (XELJANZ)							≥18 yo			
Ustekinumab (STELARA)		≥ 18 yo			≥18 yo	≥18 yo				
Vedolizumab (ENTYVIO)		≥18 yo						≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; FMF = Familial Mediterranean Fever; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Table 2. Mechanism of Action, Dosing and Formulation of Biologic Immunosuppressants

Generic Name	Maintenance Dosing	How Supplied
CD-20 Inhibitor		
Rituximab	1000 mg IV every 2 weeks x 2 doses (one course) repeated every 24 weeks	100 and 500 mg IV vials
Integrin Receptor Antagonist		
Natalizumab	300 mg IV every 4 weeks	300 mg IV vial
Vedolizumab	300 mg IV every 8 weeks	300 mg IV vial
IL-1 Receptor Antagonist		
Anakinra	100mg SC once daily	100 mg SC Injection
Canakinumab	4 mg/kg SC every 4 weeks	150 mg SC Injection
IL-6 Receptor Antagonist		
Tocilizumab	**Adults:** 4 to 8 mg/kg IV every 4 weeks Or 162 mg SC every week or every other week based on clinical response **Pediatrics**: 8-12 mg IV Infusion depending on indication and weight	80, 200 and 400 mg IV vials and 162 mg SC Injection
Sarilumab	200 mg SC every 2 weeks	150 mg and 200mg prefilled syringes
IL-12 and IL-23 Inhibitor		
Ustekinumab	Psoriasis: SC dosing varies by weight (45 mg if ≤100 kg and 90 mg if >100 kg) every 12 weeks Psoriatic Arthritis: SC dosing varies by weight (45 mg if ≤100 kg and 90 mg if >100 kg with concomitant moderate-severe psoriasis) every 12 weeks Crohn's Disease: Initial weight-based IV infusion x1 followed by 90 mg SC every 8 weeks	45 and 90 mg SC pre-filled syringe, 45 mg SC vial, and 130mg IV vial
IL-17 Receptor Antagonist		
Brodalumab	210 mg SC every 2 weeks	210 mg SC Injection
Ixekizumab	80 mg SC every 4 weeks	80 mg SC Injection
Secukinumab	SC dosing varies by indication	150 mg SC Injection
Janus Kinase Inhibitor		
Tofacitinib	5 mg po twice daily OR 11 mg XR po once daily	5 mg oral immediate release and 11 mg XR
PDE-4 Inhibitor		
Apremilast	30mg orally twice daily	10, 20 and 30 mg tablets
T Lymphocyte Inhibitor		
Abatacept	**Adults:** 500 mg to 1000 mg (dose varies by weight) IV every 4 weeks OR 125 mg SC once weekly **Pediatrics**: 10 mg/kg IV every 4 weeks (≥6 yo) OR 50 -125 mg (weight based) SC once weekly (≥2 yo)	250 mg IV vial and 125 mg SC Injection
TNF inhibitor		
Adalimumab	SC dosing varies by indication	10, 20, 40 and 80 mg SC Injection
Certolizumab	SC dosing varies by indication	200 mg SC Injection
Etanercept	50 mg SC once weekly	50 mg SC Injection
Golimumab	SC and IV dosing varies by indication	50 and 100 mg SC Injection, 50 mg/4 mL IV vial
Infliximab	3-10 mg/kg via IV infusion – dose and interval varies by indication	100 mg IV vial

Abbreviations: IL = interleukin; IM= intramuscular; IV = intravenous; kg = kilogram; mg = milligram; PDE = phosphodiesterase; po= oral; SC = subcutaneous; TNF = tumor necrosis factor; XR = extended release

Table 3. Outcomes Used for Assessment of Disease Progression in Clinical Trials[62,63]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale)	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
BASDI 50	• ≥ 50% improvement in BASDAI	
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score)	Scale of 0-10: 0 is no symptoms, 10 is very severe
ASAS20	• Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure	Assessment of response to therapy by percent in symptom improvement
ASAS40	• Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above • No worsening at all in remaining measure	
ASAS Partial Remission	• Reflects low disease activity	Value of ≤ 2 in each of the 4 domains
Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement

Psoriasis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI-75	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments
Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little , 2 a lot and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life

Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score(DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)
American College of Rheumatology (ACR) ACR 20 ACR 50 ACR 70	Definition of improvement in RA symptoms • 20% improvement in tender and swollen joint counts • 20% improvement in 3 of 5 remaining ACR core set measures ○ patient global assessment (VAS score) ○ physician global assessment (VAS score) ○ self-reported physical disability (HAQ score) ○ an acute phase reactant (ESR or CRP) ○ patient pain assessment (VAS score) • 50% improvement in tender and swollen joint counts • 50% improvement in 3 of 5 remaining ACR core set measures • 70% improvement in tender and swollen joint counts • 70% improvement in 3 of 5 remaining ACR core set measures	 20% improvement 50% improvement 70% improvement
Crohn's Disease		
Outcome Measure	**Domains**	**Scale and Scoring**
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x7) 4. Presence of complications (weight x20) 5. Use of Lomotil or opiates for diarrhea (weight x30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x6) 8. Percentage deviation from standard weight (weight x1)	Each factor is weighted and summed to achieve a total score • Scores ≤150 indicate minimal disease • Scores >150 indicate active disease • Scores >450 indicate extremely severe disease

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence review 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:
Rheumatoid Arthritis
Institute for Clinical and Economic Review
The Institute for Clinical and Economic Review (ICER) published a report in early 2017 to analyze the comparative clinical effectiveness of biologic agents in managing moderately to severely active RA.[5] FDA approved biologics included in the ICER review are: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, and tofacitinib. Two additional agents, sarilumab and baricitinib, were included in the analysis but did not have FDA approval at the time of the report. Sixty-seven RCTs and 17 observational studies met inclusion criteria. Of the RCTs, 60 focused on biologic therapy in combination with MTX or other DMARDs, 5 focused on biologic monotherapy, and 2 included both combination and monotherapy. The trials were rated as fair to good quality using US Preventative Services Task Force (UPSTF) criteria. Eight RCTs involved head-to-head comparisons, most frequently using adalimumab as the comparator agent because adalimumab was one of the first biologics to be approved for RA treatment. No studies comparing rituximab or golimumab to another biologic of interest were identified. In one head-to-head trial, tocilizumab monotherapy was found to be superior to adalimumab monotherapy in rates of clinical remission achieved at week 24 using the Disease Activity 28- Erythrocyte Sedimentation Rate (DAS28-ESR) (39.9% vs. 10.5%, respectively; $p<0.0001$) and ACR 20 (65% vs 49%; respectively; $p=0.0038$).[5] Tocilizumab did not differ from adalimumab in HAQ-DI improvement and there were no data on radiologic progression.[5] In all head-to-head trials of combination (biologic plus DMARD) therapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, ACR response and improvement in HAQ-DI.[5] Data on radiographic progression was not available for tofacitinib, certolizumab pegol or etanercept when compared to adalimumab. The results of the comparative trials of adalimumab plus DMARD versus other biologics plus DMARD therapy are summarized in **Table 4**.

Table 4. Biologics Plus DMARD vs Adalimumab Plus DMARD[5]

Drug	Low Disease Activity (DAS28-ESR)/Remission	ACR Response	Radiographic Progression	HAQ-DI (Function)
Abatacept (SC)	Comparable	Comparable	Comparable	Comparable
Tofacitinib	Comparable	Comparable	No Data	Comparable
Certolizumab Pegol	Comparable	Comparable	No Data	Comparable
Etanercept	Comparable	No Data	No Data	No Data

Abbreviations: ACR = American College of Rheumatology; Disease Activity Score = DAS; Erythrocyte Sedimentation Rate = ESR; HAQ-DI = Health Assessment Questionnaire Disability Index; SC = subcutaneous

All biologics evaluated in combination with conventional DMARDs significantly improved outcomes in disease activity, remission, and ACR response compared to conventional DMARDs alone.[5] Radiographic progression was also significantly reduced with most biologics in comparison to conventional DMARDs, but differences in the progression measures used made comparisons across studies difficult.[5] Improvements in function and disability as measured on the HAQ-DI were statistically superior for all biologics compared to conventional DMARDs.[5]

Cochrane Collaboration

A series of Cochrane reviews published in 2016 and 2017 focused on evaluating the safety and efficacy of biologics used to manage RA.[1-4] This topic was published as 4 separate reviews stratified according to drug exposure: combination of biologic therapy with MTX/DMARDs; biologics used as monotherapy after trial of MTX/DMARD; biologic-experienced patients; and biologic-naive patients. A network meta-analysis (NMA) was performed to provide more information when direct evidence was lacking. For the purposes of this update, the conclusions based on direct evidence were prioritized over the indirect analysis derived from the NMA.

The first review focused on adults with RA who received combination biologic and DMARD therapy after failure to respond to MTX or other DMARDs. Ten biologics including abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib were added to MTX or another DMARD. Comparator agents included MTX, DMARDs, placebo or a combination of DMARDs without biologic therapy evaluated over 6 to 12 months. In this update, 79 RCTs with 32,874 participants provided usable data.[1] The reviewers rated the included trials as moderate quality. The primary efficacy outcome was achievement of ACR50; defined as 50% improvement in both tender and swollen joint counts and 50% improvement in pain and disability.[1] Other outcomes included RA disease remission, withdrawals due to adverse events (AE), serious adverse events (SAEs), and incidence of cancer. Biologics in combination with MTX/DMARD were associated with a greater improvement in ACR50 versus comparator (relative risk (RR) 2.71 (95% CI 2.36 to 3.10); absolute risk reduction (ARR) 0.2; number needed to treat (NNT) = 5).[1] Participants receiving biologic + MTX/DMARD were more likely to achieve remission (defined as DAS < 1.6 or DAS-28 < 2.6) versus comparator (RR 2.81 (95% CI 2.23 to 3.53); ARR 0.18; NNT = 6) [1] Results for withdrawals due to AEs were inconclusive (RR 1.24; 95% CI 0.99 to 1.57) as was the rate of SAEs (RR 1.12; 95% CI 0.99 to 1.27) and odds of cancer (odds ratio (OR) 1.07; 95% CI 0.68 to 1.68) when biologics were evaluated with a comparator agent.[1]

A second 2016 Cochrane review utilized the same inclusion criteria and outcome parameters, but focused on adult RA patients who failed treatment with MTX or another DMARD and were switched to biologic monotherapy and treated for 6 to 12 months.[2] Comparator agents included placebo, MTX, other DMARDs, or another biologic agent. A total of 46 studies evaluated biologic monotherapy in RA patients whose treatment with MTX or DMARDs had failed.[2] The quality of trials was rated as moderate by the reviewers. Biologic monotherapy was associated with improvement in ACR50 versus placebo (RR 4.68 (95% CI, 2.93 to 7.48); ARR 0.2; NNT = 5). [2] Remission rates were also improved with biologic monotherapy RA versus placebo (RR (1.12; 95% CI 1.03 to 1.22); ARR 0.1; NNT = 10).[2] Results for withdrawals from biologic monotherapy due to AEs and SEAs were inconclusive when compared to placebo (RR 1.65; 95% CI 0.97 to 2.79 and RR 1.21; 95% CI 0.71 to 2.07, respectively).[2] No data were available for cancer incidence for monotherapy versus placebo comparisons.

The third update in this series, published in 2017, focused on biologic therapy in people with RA who had previously been treated unsuccessfully with biologic agents.[3] This update included 9 new RCTs for a total of 12 RCTs that included 3364 participants. Data were available for 4 of the TNF inhibitors (certolizumab pegol, etanercept, golimumab, and infliximab) and 3 of the non-TNF biologics (abatacept, rituximab, and tocilizumab); and one study provided data for

tofacitinib.[3] The comparator was placebo in 3 RCTs (n = 548 participants), MTX or other traditional DMARD in 6 RCTs (n = 2468 participants), and another biologic in 3 RCTs (n =348 participants).[3] The majority of the trials lasted less than 12 months. The authors graded the quality of the evidence for most outcomes as moderate or low due to study limitations, heterogeneity, or rarity of direct comparator trials.[3] Compared to placebo, biologics were associated with significant improvement in RA as demonstrated by higher ACR50 (RR 4.10 (95% CI 1.97 to 8.55); ARR 0.14; NNT = 7) and rates of remission (RR 13.51 (95% CI 1.85 to 98.45); ARR = 0.09; NNT = 11).[3] Results for withdrawals due to AEs and SAEs did not show any significant differences. There were no studies available for analysis of cancer outcomes. Compared to MTX or other traditional DMARDs, biologic plus MTX was associated with significant improvement in ACR50 (RR 4.07 (95% CI 2.76 to 5.99); ARR = 0.16; NNT = 7) and remission rates (RR 20.73 (95% CI 4.13 to 104.16); ARR = 0.10; NNT = 10) among the biologic plus MTX group compared to MTX or other DMARDs.[3] Results were not significantly different for withdrawals due to AEs or SEAs, and were inconclusive for cancer.

The final systematic review in this series published in 2017 evaluated biologics for RA patients naive to MTX.[4] Nineteen RCTs with 6485 participants met inclusion criteria and data were available for four TNF biologics: adalimumab (6 studies; 1851 participants), etanercept (3 studies; 678 participants), golimumab (1 study; 637 participants) and infliximab (7 studies; 1363 participants)) and two non-TNF biologics (abatacept (1 study; 509 participants) and rituximab (1 study; 748 participants)).[4] In all trials MTX was the comparator agent. Less than 50% of the studies were at low risk of bias for appropriate randomization methods and blinding, only 21% were at low risk for selective reporting, 53% had low risk of bias for attrition and 89% had low risk of bias for major imbalance at baseline.[4] Trial durations ranged from 6 to 24 months. Half of the trials contained participants with early RA (less than two years' duration) and the other half included participants with established RA (2 to 10 years). In traditional meta-analyses, there was moderate-quality evidence that biologics with MTX were associated with statistically significant and clinically meaningful benefit versus comparator as demonstrated by ACR50 and RA remission rates.[4] Biologic therapy with MTX had a RR of 1.40 for ACR50 (95% CI 1.30 to 1.49); ARR 0.16; NNT = 7.[4] For RA remission rates, biologic therapy with MTX had a RR of 1.62 (95% CI 1.33 to 1.98), ARR 0.15; NNT = 6.[4] Biologic therapy with MTX was also associated with a significant, but modest -0.10 improvement in HAQ scores (95% CI -0.16 to -0.04 on a 0 to 3 point scale), with ARR = 0.3% and NNT = 4 versus MTX.[4] Results were inconclusive for withdrawals due to AEs, SAEs, and risk of cancer.

In conclusion, the 3 systematic reviews focused on safety and efficacy of biologic agents in RA patients who failed DMARD or biologic therapy showed that compared to placebo or DMARD therapy, biologics improve RA remission rates and response to therapy as measured by ACR 50. Withdrawals due to AEs, rates of cancer occurrence, and rates of SAEs were inconclusive. The final systematic review in MTX-naive RA participants, also found that compared with MTX alone, biologics in combination with MTX were associated with greater ACR50, HAQ scores, and RA remission rates compared to monotherapy with MTX.

Ankylosing spondylitis

Cochrane Collaboration

A 2015 Cochrane systematic review compared TNF inhibitors for ankylosing spondylitis.[6] Twenty-one, short-term (24 weeks or less) RCTs with a total of 3308 participants were identified. Eighteen studies contributed data to the meta-analysis: adalimumab (4 studies), etanercept (8 studies), golimumab (2 studies), infliximab (3 studies), and one head-to-head study (etanercept versus infliximab) which was unblinded with unclear randomization and therefore considered at a higher risk of bias.[6] The risk of selection and detection bias was low or unclear for most of the studies.[6] The majority of the studies were funded by pharmaceutical companies. Most studies permitted concomitant therapy of stable doses of DMARDs, non-steroidal anti-inflammatory drugs, or corticosteroids, but allowances varied across studies.[6] One outcome measure was the Assessment in ASAS40 defined as ≥ 40% improvement and ≥ 2 units absolute improvement (range 1–10) in 3 of 4 domains: functional status, spinal pain, global disease activity, and inflammation (as measured by the mean of intensity and duration of morning stiffness), without deterioration in the remaining domain.[24] Improvement in physical function on a 0 to 10 scale and ASAS remission rates were also evaluated.

Compared with placebo, there was high quality evidence that patients on a TNF inhibitor were 3 to 4 times more likely to achieve an ASAS40 response by 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95% CI 2.80 to 5.74), with a 25% to 40% absolute difference between treatment and placebo groups.[6] The NNT to achieve an ASAS 40 response at 6 months ranged from 3 to 5.[6] There was high quality evidence of improvement in physical function on a 0 to 10 scale (adalimumab: mean difference (MD) -1.6, 95% CI -2.2 to -0.9; etanercept: MD -1.1, 95% CI -1.6 to -0.6; golimumab: MD -1.5, 95% CI -2.3 to -0.7; infliximab: MD -2.1, 95% CI -2.7 to -1.4, with an 11% to 21% absolute difference between treatment and placebo groups.[6] The NNT to achieve the minimally clinically important difference of 0.7 points ranged from 2 to 4.[6] Compared with placebo, there was moderate quality evidence that patients on a TNF inhibitor were more likely to achieve an ASAS partial remission (defined as a value < 2 on a 0 to 10 point scale) by six months (adalimumab: RR 6.28, 95% CI 3.13 to 12.78; etanercept: RR 4.24, 95% CI 2.31 to 8.09; golimumab: RR 5.18, 95% CI 1.90 to 14.79; infliximab: RR 15.41, 95% CI 5.09 to 47.98 with a 10% to 44% absolute difference between treatment and placebo groups. The NNT to achieve an ASAS partial remission response ranged from 3 to 11.[6] The single head to head trial of etanercept versus infliximab was conducted in a small population (n=50), unblinded and contained incomplete randomization details. The results were unclear and difficult to interpret.

There were few events of withdrawals due to adverse events leading to imprecision around the individual estimates. When all the TNF inhibitors were combined against placebo, there was moderate quality evidence from 16 studies of an increased risk of withdrawals due to AEs in the TNF inhibitor group (OR 2.44, 95% CI 1.26 to 4.72; total events: 38/1637 in biologic group; 7/986 in placebo) though the absolute increase in harm was small (1%; 95% CI 0% to 2%).[6] Due to low event rates, differences in SAEs between individual TNF inhibitors against placebo or for all 4 biologics pooled together versus placebo was inconclusive. For all TNF inhibitors pooled versus placebo based on 16 studies: OR 1.45, 95% CI 0.85 to 2.48; 51/1530 in biologic group; 18/878 in placebo; absolute difference: 1% (95% CI 0% to 2%), NNH = 100.[6]

National Institute for Health and Care Excellence

The British National Institute for Health Research (NIHR) funded a 2016 systematic review focused on the safety and clinical effectiveness of TNF inhibitors used to treat AS and nonradiographic axial SpA.[24] Evidence for the following biologic agents was evaluated: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Studies published through July 2014 were reviewed for inclusion. In total, 28 eligible RCTs were identified. Twenty two trials were placebo controlled (mostly up to 12 weeks) and 17 of those trials extended into open-label active treatment-only phases.[24] Most RCTs were judged to have a low risk of bias overall by the reviewers.[24] Disease activity was measured by the BASDAI score consisting of a 1–10 scale (1 being no problem and 10 being the worst problem) to answer questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness duration, and morning stiffness severity. Function was assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) tool to assess ability to perform activities on a 10-point scale (1 is easy and 10 is impossible) for daily functions: putting on socks, bending from the waist, reaching, getting up from a chair or the floor, standing unassisted, climbing stairs, and exercise. A BASDI 50 response indicates a greater than or equal 50% improvement in BASDI score. Two additional outcome measures included the proportion of patients who achieved improvement in ASAS20 and ASAS40 scores. ASAS40 scores demonstrate 40% improvement in AS domains while ASAS20 scores show a 20% response in AS domains.

In patients with AS, results showed consistent effects across the different anti-TNFs when compared with placebo over 10 to 16 weeks: for ASAS-20 the pooled relative risks ranged from 1.80; 95% CI 1.24 to 1.39 (certolizumab pegol) to 2.45; 95% CI 1.73 to 3.06 (infliximab); for ASAS-40 the relative risks ranged from 2.53 95% CI 1.47 to 3.98 (certolizumab pegol) to 3.42; 95% CI 2.57 to 4.55 (adalimumab) and for BASDAI 50 the relative risks ranged from 3.16; 95% CI 2.40 to 4.16 (adalimumab) to 4.86; 95% CI 2.41 to 7.82 (infliximab).[24] Adalimumab, certolizumab pegol, etanercept and infliximab produced significant reductions in disease activity, with BASDAI reductions ranging from 1.46 units; 95% CI -2.17 to -0.74 (certolizumab pegol) to 2.28 units; 95% CI -3.18 to -1.38 (infliximab), and function, with BASFI reductions ranging from 1.1 units: 95% CI -1.83 to -0.37(certolizumab pegol) to 2.16 units; 95% CI -3.18 to -1.12 (infliximab).[24] When

analyzed as a class, TNF inhibitors were statistically significantly more likely than placebo to result in patients with AS achieving an ASAS 20 response (RR = 2.21), an ASAS 40 response (RR = 3.06), and a BASDAI 50 response (RR = 3.37).[24] They also produced statistically significant improvements (calculated using mean difference in change from baseline) in disease activity (BASDAI mean difference = –1.66 units) and in function (BASFI mean difference = –1.38 units).[24]

For the nonradiographic axial SpA population, five RCTs were included in the short term 10 to 16 week analysis. When TNF inhibitors were considered as a class, statistically significant improvements were found for ASAS 20 (RR = 1.65); ASAS 40 (RR = 2.74); BASDAI 50 (RR = 2.31); BASDAI (mean difference = –1.32 units); and BASFI (mean difference = –0.99 units).[24] For the disease activity, function and responder outcomes, these common class efficacy estimates were consistently slightly smaller for nonradiographic axial SpA than for AS, most noticeably for BASFI and BASDAI 50.[24]

Overall, the number and size of trials, and the short duration of their placebo-controlled phases, were too limited to provide enough data for meaningful analyses of AEs.[24] When individual TNF inhibitors were analyzed, only infliximab and certolizumab pegol were associated with statistically significant increases in AEs compared with control treatments Infliximab was associated with higher rates of total AEs (NNH 13; 95% CI 8 to 505) and withdrawals because of AEs (NNH 10; 95% CI 5 to 30). Certolizumab pegol was associated with higher rates of serious infections (NNH 12; 95% CI 4 to 79) and SAEs (NNH 18; 95% CI 9 to 162).[24]

In summary, for treatment of AS, TNF inhibitors can be assumed to have a class effect, with no evidence to support clinical superiority of one agent in over another. Effectiveness appears to be maintained over time in about 50% of patients at 2 years. Evidence for an effect of TNF inhibitors delaying disease progression was limited; results from ongoing long-term studies should help to clarify this issue.[6]

Plaque Psoriasis

Institute for Clinical and Economic Review

ICER published a systematic evaluation of the biologics for the treatment of moderate to severe PsO in late 2016.[7] A total of 80 references met inclusion criteria including 36 RCTs and 11 observational studies. Eight studies were head-to-head comparative evaluations of biologic agents for plaque psoriasis. The primary outcome for all RCTs of biologic therapy was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent), after which treatment crossover was typically allowed.[37] Long-term effectiveness and safety data were variably reported by individual drug. The primary outcome was the percentage of patients who achieved a 75% reduction in the PASI score (PASI 75). PASI 100 indicates full disease clearance. Adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab and apremilast all showed significantly higher PASI 75 response rates when compared to placebo at the end of the induction period (10 to 16 weeks depending on the drug) as presented in **Table 5.**[7]

Table 5. Placebo Controlled Trials: Range of PASI 75 Response Rates at 10 to 16 weeks[7]

Drug	PASI 75	
	Treatment % Response	**Placebo % Response**
Adalimumab	71-80	7-19
Etanercept	40-59	3-7
Infliximab	76-80	2-3
Ustekinumab 45 mg	67	3-4
Ustekinumab 90 mg	66-76	3-4
Secukinumab	76-87	0-5

Brodalumab	83-86	3-8
Apremilast	29-33	5-6

In direct comparative trials, response rates from ustekinumab, secukinumab, and ixekizumab were superior to etanercept, as measured by the PASI 90 and 100. Additionally, secukinumab and brodalumab were superior to ustekinumab.[7] The response rates from the comparative trials are outlined in **Table 6.**

Table 6. Comparative Trials: PASI Response Rates at 10-16 Weeks[7]

Trial	Treatment	PASI 75 %	PASI 90 %	PASI 100 %
ACCEPT[64]	Etanercept	57	23	NR
	Ustekinumab 45 mg	68	36	NR
	Ustekinumab 90 mg	74	45	NR
FIXTURE[65]	Etanercept	44	21	4
	Secukinumab 300mg	77	54	24
UNCOVER 2 & 3[66]	Etanercept	42-53	19-26	5-7
	Ixekizumab	87-90	68-70	38-41
AMAGINE 2 & 3[9]	Ustekinumab weight based dosing	69-70	47-48	19-22
	Brodalumab 210 mg	85-86	69-70	37-44
CLEAR[67]	Ustekinumab weight based dosing	79	53	26
	Secukinumab 300mg	91	73	39

Severe or SAEs were rarely reported during the induction phase of treatment. Infections (e.g., nasopharyngitis, upper respiratory tract infections, etc.), injection site or infusion reactions, headache, and nausea were the most common AEs with biologics. Infliximab appears to have higher rates of these events than other biologics.[7] For psoriasis, in 1-year follow-up of pivotal trials of etanercept, ustekinumab, secukinumab, and brodalumab had comparable safety profiles. For example, the biologics have rates of AEs leading to discontinuation of between 1.2 and 3.2 per 100 person-years; rates of serious adverse effects of between 4.0 and 13.0 per 100 person-years; and rates of serious infections between 0.8 and 1.0 per 100 person-years. In 5-years of follow up, ustekinumab continues to have comparable AE rates.[7] In an analysis from a registry of 11,466 psoriasis patients with 22,311 person-years of follow-up focused on the rate of severe infectious complications, infliximab had a higher rate of serious infections (2.78 per 100 person-years) and ustekinumab (0.95 per 100 person-years) had a lower rate of serious infections than other biologics and other systemic psoriasis treatments (1.26 to 1.80 per 100 person-years).[7]

Cochrane Collaboration

A 2015 Cochrane review evaluated the safety and efficacy of TNF inhibitors for the treatment of pediatric psoriasis (PP).[68] The literature search evaluated publications through July 2015. Three TNF inhibitors (etanercept, infliximab and adalimumab) are approved to treat inflammatory disorders in children. This review focused on any children under 18 years of age with chronic PP who had not responded to DMARD pharmacotherapy or phototherapy. Only one RCT met inclusion criteria and included 211 participants with pediatric PP aged 4 to 17 years who received etanercept or placebo over 48 weeks. The study was rated at low risk of bias. At week 12 (short term), 60 out of 106 participants (57%) who received etanercept achieved PASI 75 compared to 12 out of 105 (11%) who received placebo (RR 4.95, 95% CI 2.83 to 8.65).[68] The absolute risk reduction with etanercept was 45% (95% CI 33.95 to 56.40; NNT = 3).[68] Current guidelines on the management of psoriasis with systemic therapy have focused mainly on adults, and there is a paucity of studies of therapies for children with moderate to

severe psoriasis.[68] Available studies are descriptive studies or case series. Therefore, more well-performed RCTs are needed to provide additional evidence for systemic treatments in children with moderate to severe psoriasis.[68]

Psoriatic Arthritis

There were not new systematic reviews or comparative evidence identified to assess the efficacy of biologics in the treatment of psoriatic arthritis since the last review.

New Guidelines:

Rheumatoid Arthritis

National Institute for Health and Care Excellence

The NICE guidelines on treating adults with RA -were updated in 2016.[69] Recommended biologics to manage RA are adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. Recommendations are as follows:[69]

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
    - disease is severe, that is, a disease activity score (DAS-28) greater than 5.1 and
    - disease has not responded to intensive therapy with a combination of conventional DMARDs.[69]
- Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance when the disease is severe and has not responded to intensive therapy with DMARDs.[69]

NICE recommendations for using certolizumab pegol to treat rheumatoid arthritis after inadequate response to a TNF inhibitor are as follows:[70]

- Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if:
    - disease activity is severe and
    - rituximab is contraindicated or not tolerated.[70]
- Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if:
    - disease activity is severe and
    - rituximab is contraindicated or not tolerated.[70]

Juvenile Idiopathic Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating JIA in children, young people and adults with abatacept, adalimumab, etanercept or tocilizumab was published December 2015.[71] This document replaced a previous document focused on the use of etanercept for the treatment of JIA published in 2002. The recommendations are as follows:

- Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorizations, as options for treating polyarticular JIA, including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is:
    - for abatacept, people 6 years and older whose disease has responded inadequately to other DMARDs including at least 1 TNF inhibitor
    - for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD
    - for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, MTX

- for tocilizumab, people 2 years and older whose disease has responded inadequately to previous therapy with MTX[71]

- Adalimumab and etanercept are recommended, within their marketing authorizations, as options for treating enthesitis-related JIA, that is, for people 6 years and older (adalimumab) and 12 years and older (etanercept) whose disease has responded inadequately to, or who are intolerant of, conventional therapy.[71]
- Etanercept is recommended, within its marketing authorization, as an option for treating psoriatic JIA, that is, in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, MTX.[71]

Ankylosing Spondylitis

National Institute for Health and Care Excellence

NICE guidance for the use TNF inhibitors in ankylosing spondylitis and non-radiographic axial spondyloarthritis was published in early 2016.[72] The guidance was based upon a systematic review funded by NIHR.[24]

- Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorizations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their National Health Service (NHS) clinician consider it appropriate to stop.[72]
- Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorizations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.[72]
- The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.[72]
- The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:
  - a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
  - a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more[72]
- Treatment with another TNF inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF inhibitor, or whose disease has stopped responding after an initial response.[72]

Plaque Psoriasis

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe PsO with ustekinumab was updated March 2017.[73] Recommendations are as follows:

- Ustekinumab is recommended as a treatment option for adults with PsO when the following criteria are met:
  - The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10.
  - The psoriasis has not responded to standard systemic therapies, including cyclosporine, MTX and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.[73]

- Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.[73]

NICE guidance regarding the use of ixekizumab for treating moderate to severe plaque PsO is as follows:[74]

- Ixekizumab is recommended as an option for treating PsO in adults, only if:
  - the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - the disease has not responded to standard systemic therapies, for example, cyclosporine, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them.[74]
- Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DQLI from when treatment started.[74]

Psoriatic Arthritis

National Institute for Health and Care Excellence

NICE guidance regarding ustekinumab for treating active PsA was updated March 2017.[75]

- Ustekinumab is recommended as an option, alone or in combination with MTX, for treating active PsA in adults only when:
  - the person has had treatment with 1 or more TNF inhibitors[75]
- Ustekinumab treatment should be stopped if the person's PsA has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis[76], people whose disease has a PASI 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.[75]

NICE guidance regarding the role of apremilast for treating active PsA was published in February 2017.[77]

- Apremilast, alone or in combination with DMARDs is recommended as an option to treat active PsA in adults only if:
  - they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
  - their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination.[77]
- Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response using the PsARC, defined as an improvement in at least 2 of the 4 PsARC criteria (including joint tenderness or swelling score) with no worsening in any criteria. If the disease has a PASI 75 response, a dermatologist should decide whether to continue treatment with apremilast after 16 weeks based on skin response.[77]

NICE guidance regarding certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs was published May 2017.[78]

Certolizumab pegol alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2)[76] or
- the person has had a TNF inhibitor but their disease has stopped responding after the first 12 weeks.[78]

Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2)[76] or
- the person has had a TNF inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks.[78]

Assess the response to certolizumab pegol and secukinumab after 12 weeks and 16 weeks of treatment respectively. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 PsARC criteria; 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a PASI 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response.[78]

Ulcerative Colitis

National Institute for Health and Care Excellence

NICE recommendations for treating UC after failure of conventional therapy with infliximab, adalimumab, and golimumab are as follows:[79]

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorizations, as options for treating moderately to severely active UC in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.[79]
- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).[79]
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active UC in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.[79]
- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient,
    - They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
    - They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again[79]

NICE guidance focused on vedolizumab for treating moderately to severely active UC published in 2015.[59]

- Vedolizumab is recommended, within its marketing authorization, as an option for treating moderately to severely active ulcerative colitis in adults.[59]
- Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see

whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.[59]

New Formulations or Indications:

1. Ustekinumab (Stelara®) for injection received expanded indications by the FDA in September 2016 for the treatment of adults with moderate to severe CD in patients who have failed other treatments.[80] The approval was based on 3 placebo-controlled RCTs (UNITI-1, UNITI-2 and IM-UNITI). UNITI-1 included 741 patients with CD in whom TNF inhibitor therapy had failed or unacceptable adverse effects occurred.[81] The UNITI-2 trial included 628 patients in whom conventional therapy failed or unacceptable side effects occurred. In both trials, patients were randomized to placebo, ustekinumab 130 mg IV, or approximately 6 mg/kg based on weight (260 mg for ≤55kg, 390 mg for 55kg to 85kg, and 520 mg for >85kg). Three hundred ninety seven patients who responded to the induction dose were enrolled in a follow-up maintenance dosing trial (IM-UNITI) of 90mg subcutaneously every 8 to 12 weeks. The primary end point for the induction trials was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The primary end point for the maintenance trial was remission at week 44 (CDAI score <150). The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo (in UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with P≤0.003 for both comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with P<0.001 for both doses).[81] In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo (P = 0.005 and P = 0.04, respectively).[81] Within each trial, adverse-event rates were similar among treatment groups.

2. The approved age for which subcutaneous abatacept (Orencia®) can be administered was lowered from 6 to 2 years for patients with polyarticular JIA by the FDA effective March 2017.[82] Dosing is weight based and ranges from 50 mg (10 to < 25kg), to 87.5mg (≥ 25 to < 50 kg) to 125 mg (≥ 50 kg) once a week. The intravenous dose continues to be limited to ages 6 years and over because it has not been studied in younger patients.[82] Clinical studies of abatacept in juvenile patients started with the JIA-1 study.[83] JIA-1 was a 3 part multi-center study in 190 pediatric patients with moderate to severe polyarticular JIA who had an inadequate response to DMARD therapy. Subjects were aged 6-17 years with a disease duration of approximately 4 years. During the open label induction phase all patients were administered intravenous abatacept 10 mg/kg on days 1, 15, 29, 57, and 85 during a 4 month period. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables.[82] At the conclusion of the induction period, pediatric ACR 30/50/70 responses to intravenous abatacept were 65%, 50%, and 28%, respectively.[82] After the open label lead induction trial, patients that demonstrated an ACR Pedi 30 response were randomized to either abatacept or placebo for 6 months or until disease flare. One hundred twenty three patients participated in the second 6 month phase in which they received intravenous abatacept 10mg/kg every 28 days.[83] During the double-blind randomized phase, abatacept-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53% respectively); 95% CI 15- 52 (p = 0.003).[82] The risk of disease flare among patients continuing on abatacept was less than one-third than that for patients withdrawn from abatacept treatment (hazard ratio=0.31; 95% CI 0.16 - 0.59)[82] Overall frequency of adverse events in the 4-month, lead-in, open-label period of the JIA-1 study was 70%; infections occurred at a frequency of 36%.[82] The most common infections were upper respiratory tract infection and nasopharyngitis. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.[82] Subjects were given the option to continue open label treatment in a 5 year follow-up treatment period.

Study JIA-2 was an open-label study with a 4-month short-term period and a long-term extension period that assessed the pharmacokinetics, safety, and efficacy of subcutaneous abatacept in 205 pediatric patients, 2 to 17 years of age with JIA.[82] Subjects had a mean disease duration of 2.5 years. The JIA-2 study is not

published and details of this trial were accessed from the abatacept manufacturer's prescribing information.[82] JIA ACR 30/50/70 responses to subcutaneous abatacept were assessed at 4 months in the 2- to 17-year-old patients and were consistent with the results from the intravenous study, JIA-1.[82] The safety experience and immunogenicity for abatacept administered subcutaneously were consistent with the intravenous Study JIA-1.[82]

3. Adalimumab received expanded indications from the FDA to treat non-infectious uveitis in adult patients.[84] The approval was based on a Phase 3, multicenter, double-blinded, placebo-controlled RCT conducted 62 study sites in 21 countries.[84] Adults with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10–35 mg/day of prednisone were randomly assigned to receive either subcutaneous adalimumab (loading dose 80 mg; biweekly dose 40 mg) or placebo, with a mandatory prednisone taper from week 2.[84] The primary efficacy endpoint was time to treatment failure, a multicomponent endpoint encompassing new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and visual acuity.[84] A total of 229 patients received placebo (n=114) or adalimumab (n=115). Median follow-up time was 155 days in the placebo group and 245 days in the adalimumab group. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.[84] Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (>18 months vs 8.3 months; hazard ratio (HR) 0.57, 95% CI 0·39–0·84; p=0.004).[84] The most common adverse events were arthralgia, nasopharyngitis, and headache.

4. Canakinumab (Ilaris®) received 3 new indications from FDA as of September 2016: 1) tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and familial Mediterranean fever (FMF). These 3 conditions are rare, but serious autoimmune diseases that can occur in children and adults. The approval was based on preliminary results from Study NCT02059291 which evaluated the safety and efficacy of canakinumab in patients with hereditary periodic fevers. The Phase 3 trial (TRAPS, HIDS/MKD, and FMF Study 1) enrolled 185 patients older than 28 days, is ongoing and is sponsored by the manufacturer. Three cohorts (TRAPS, HIDS/MKD, and FMF) were assigned as follows: a 12-week screening period (Part 1), followed by a 16 week, randomized, double-blind, placebo-controlled parallel-arm treatment period (Part 2), followed by a 24-week randomized withdrawal period (Part 3), followed by a 72-week, open-label treatment period (Part 4). [85] The primary outcome measure was the percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment period (16 weeks). Resolution of the initial disease flare was defined as: Physical Global Assessment of Disease activity (PGA) <2 and C-reactive protein (CRP) within normal range (<= 10 mg/L) or reduction by at least 70% from baseline. The PGA was evaluated by the investigator based on a 5-point scale: 0 = none (no) disease associated with clinical signs and symptoms; 1 = minimal disease associated signs and symptoms; 2 = mild disease associated signs and symptoms; 3 = moderate disease associated signs and symptoms; and 5 = severe disease associated signs and symptoms. Results are presented in **Table 7**.

Table 7: Proportion of TRAPS, HIDS/MKD, AND FMF patients who achieved a complete response (resolution of index flare by day 15 and maintained through week 16).[85]

Cohort	Canakinumab 150mg n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	p-value
TRAPS	10/22 (45.5%)	2/24 (8.3%)	9.17 (1.51 to 94.61)	P = 0.005
HIDS/MKD	13/27 (35.1%)	2/35 (5.7%)	8.94 (1.72 to 86.41)	P = 0.002
FMF	19/31 (61.3%)	2/32 (6.3%)	23.75 (4.38 to 227.53)	P < 0.001

Abbreviations: n = number of patients with response; N= number of patients evaluated for that response in each cohort; CI = confidence interval

5. The FDA approved etanercept (Enbrel®) to treat pediatric patients 4 years and older with chronic moderate-to-severe PsO who are candidates for systemic therapy or phototherapy; prior to this approval only adults aged 18 years and older were approved for this indication. A 48-week, randomized, double-blind, placebo-controlled study enrolled 211 pediatric subjects 4 to 17 years of age, with moderate to severe PsO inadequately controlled on topical therapy. Response

to treatment was assessed after 12 weeks of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. At twelve weeks 57% of patients had a reduction of PASI 75 compared to 11% of patients in the placebo arm (confidence intervals not reported).[86]

6. Inflectra® (infliximab-dyyb or CT-P13) was approved by the FDA in April 2016 as a biosimilar of Remicade® (infliximab).[87] Biosimilar guidelines issued by the FDA in the U.S. state that demonstration of clinical comparability between a biosimilar and its innovator requires completion of comparator clinical trials assessing pharmacokinetics (PK), efficacy, and safety.[88] Two pivotal trials, PLANETRA and PLANETAS, conducted in RA and AS patients respectively, provided data for infliximab-dyyb approval in the US. PLANETRA was a multinational, phase 3, double-blind RCT that evaluated the safety and efficacy of infliximab with the biosimilar formulation (CT-P13) in 606 RA patients for up to 54 weeks.[89] Efficacy endpoints included ACR20, ACR50 and ACR70 response rates, DAS28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). Immunogenicity, safety, PK, and pharmacodynamic (PD) outcomes were also assessed. At week 54, ACR20 response rate was highly similar between groups (CT-P13 = 74.7 %, infliximab = 71.3 %).[89] ACR50 and ACR70 response rates were also comparable between CT-P13 (43.6 % and 21.3 %, respectively) and infliximab (43.1 % and 19.9 %, respectively).[89] DAS28, SDAI, and CDAI decreased from baseline to week 54 to a similar extent with CT-P13 and infliximab.[89] The proportion of patients positive for antidrug antibodies at week 54 was similar between the two groups: 41.1 % and 36.0 % with CT-P13 and infliximab, respectively.[89] CT-P13 was well tolerated and had a similar safety profile to infliximab. PK/PD results were also comparable between CT-P13 and infliximab.[89]

The second RCT that compared CT-P13 to infliximab (the PLANETAS trial) was conducted in 250 AS patients.[90] Efficacy endpoints included ASA20, ASAS40, and ASAS partial remission, BASDAI, and BASFI score changes from baseline to 54 weeks after treatment. At week 54, ASA20, ASA40 and ASAS partial remission were comparable between the 2 treatment groups. Change in mean BASDAI (CT-P13= -3.1 versus infliximab = −2.8) and mean BASFI (CT-P13 = −2.9 versus infliximab = –2.7) from baseline to week 54, were also similar between treatment groups.[90] There was no notable difference between treatment groups in the incidence of adverse events, serious adverse events, infections, or infusion-related reactions.[90]

According to the manufacturer's prescribing information, infliximab-dyyb is FDA approved to manage RA, AS, PsA, UC and PsO in adults and CD in adult and pediatric patients.[87] Only infliximab is FDA approved to treat pediatric UC. The pediatric UC indication is protected by orphan drug exclusivity until September 2018.[91] Therefore, infliximab-dyyb does not have FDA approval to manage UC in children and is only FDA approved to manage adult UC.[87]

7. Alefacept was voluntary removed from the U.S. market in 2011 by the manufacturer because it had fallen out of favor for more effective therapies for treatment of psoriasis.

8. Oral methotrexate oral solution (Xatmep™) from Silvergate Pharmaceuticals, Inc. received FDA approval April 2017.[92] It is a ready-to-use 2.5mg/ml oral formulation that must be refrigerated until it is dispensed. After dispensing, the product can be stored at room temperature for 60 days. Methotrexate oral solution is indicated for the management of pediatric patients with JIA and acute lymphoblastic leukemia (ALL).

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

Randomized Controlled Trials: A total of 198 citations were manually reviewed from the initial literature search. After further review, 198 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: Brodalumab (Siliq®)

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:
Brodalumab was approved for PsO on the basis of 3 randomized, multicenter, double-blind, placebo-controlled phase 3 trials (AMAGINE-1, 2 and 3).[10] Two trials (AMAGINE-2 and 3) also included patients randomized to an active comparator, ustekinumab. Primary endpoints for these trials included the proportion of patients with a 75% improvement in PASI (PASI75) and proportion of patients with a sPGA score of 0 or 1. The proportion of patients achieving a 100% improvement in PASI (PASI100), indicating completely clear skin, was also used as a primary endpoint when compared to ustekinumab.[9] Secondary endpoints included patients with total PSI scores of 8 or less with no single item rated greater than 1.[9] Endpoints were assessed at 12 weeks with continued follow-up and maintenance treatment through 52 weeks. In AMAGINE-1, patients initially randomized to brodalumab groups were re-randomized to brodalumab or placebo after 12 weeks. Patients were treated with open-label brodalumab with disease re-emergence (defined as a sPGA score >2). In AMAGINE-2 and 3 after 12 weeks, patients were re-randomized to one of 4 maintenance regimens: brodalumab 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks.[38] Patients initially randomized to ustekinumab continued on therapy unless sPGA remained greater than 2, in which case patients were switched to brodalumab 210 mg every 2 weeks.[38]

The majority of patients included in these trials were white males with an average age of 43-45 years and approximately 15% had a history of depression.[9,38] Patients with PsO may experience co-morbid depression due to the psychological burden of visible disfiguration.[93] The mean duration of psoriasis was 18-20 years.[38] In AMAGINE-1, 46% of patients had prior treatment with a biologic agent.[38] In AMAGINE-2 and 3, approximately 76% of patients had prior systemic therapy and 29% had prior biologic therapy.[9,38] Disease severity was classified using 3 different scales: sPGA, PASI and PSI. The majority of patients has sPGA scores of 3 or 4 and the average PAS score was 20, indicating moderate or severe disease. On average, patients had disease impacting 27% of their body surface area. Patients were excluded from the trial if they had current infection or history of serious infection, Crohn's disease, history of myocardial infarction or unstable angina within the past year or history of malignancy. Patients were also excluded if they had other clinically significant, uncontrolled comorbid conditions.

Overall, studies were well designed with adequate randomization, blinding, and appropriate data analysis. However, large differences in symptom improvement between brodalumab and placebo could easily lead to unblinding of treatment groups increasing risk of performance and detection bias. In addition, the manufacturer of brodalumab was involved in multiple aspects of the study and performed an unblinded data analysis increasing risk of reporting bias.

In all phase 3 trials, use of brodalumab 210 mg every 2 weeks demonstrated consistent symptom improvement compared to placebo after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. More patients treated with brodalumab achieved a 75% improvement in PASI compared to placebo (ARR of 81%, 78%, and 79% for AMAGINE-1, -2, and -3, respectively).[9,38] Subgroup analysis based on gender, age, race, weight, prior biologic use and region also demonstrated similar results, and similar improvements were observed proportion of patients with sPGA scores of 0 or 1.[9,38] Complete skin clearance as evaluated by PASI 100 or sPGA of 0 was achieved in approximately 37-44% of patients compared to placebo.[9,38] Patient-reported symptom improvement (PSI≤8) was also consistently improved with use of brodalumab 210 mg every 2 weeks compared to placebo (ARR of 55% to 61%).[9,38] Compared to ustekinumab, brodalumab 210 mg every 2 weeks demonstrated a statistically significant improvement in PASI 100 (complete skin clearance) in both AMAGINE-2 (37% vs. 19%,

ARR 18%, NNT 6, p<0.001) and AMAGINE-3 (44% vs 22%, ARR 22%, NNT 5, p<0.001).[38] At a lower dose of 140 mg every 2 weeks, brodalumab did not demonstrate consistent improvement compared to ustekinumab in both trials. Similar improvements, as well as dose related effect, were documented in a high quality systematic review of brodalumab compared to placebo.[94]

In AMAGINE-1, patients were re-randomized at week 12 to receive placebo or to continue their originally assigned brodalumab dose. Of the patients with treatment success at week 12, 83% maintained a sPGA response of 0 or 1 compared to approximately 2% of subjects receiving placebo at 52 weeks (p<0.001; ARR 81%, 95% CI not reported).[9,38] In AMAGINE-2 and AMAGINE-3, patients were re-randomized to various dosing regimens of brodalumab. In patients receiving the FDA approved dose of 210 mg every 2 weeks, 79% of initial responders maintained a sPGA response of 0 or 1.[38] Comparative efficacy of brodalumab to placebo or ustekinumab at week 52 was only evaluated descriptively. Patients receiving ustekinumab to 52 weeks had a higher maintenance response than patients receiving brodalumab 140 mg every 2 weeks, but a lower response than patients receiving brodalumab 210 mg every 2 weeks.[38]

Clinical Safety:

The safety analysis for brodalumab included a total of 5205 patients with moderate to severe plaque psoriasis who received at least 1 dose of brodalumab enrolled in clinical trials and open-label extension studies.[95] This population included 4145 patients exposed to brodalumab for at least 3 months and 1220 patients who received brodalumab for at least 18 months.[95] Rates of the most common adverse effects associated with the FDA approved dose of brodalumab occurring in clinical trials up to 12 weeks are listed in **Table 8.** The most frequent serious adverse effects occurring in brodalumab treatment groups at 12 weeks included cellulitis, appendicitis, acute pancreatitis, and gastroenteritis (incidence ranging from 0.1% to 0.2%).[95] Upon comparison to ustekinumab at 52 weeks, patients receiving brodalumab had similar rates of serious adverse events (8.5 vs. 8.3 per 100 subject-years, respectively).[95] Adverse events occurring in more than 1 patient which lead to discontinuation of treatment included neutropenia, arthralgias, and urticaria.[95] During the course of the clinical trial program, 13 patients who had received brodalumab died due to cardiovascular related events.[95] Similarly, at 52 weeks, cardiovascular events were more frequent in patients who had received brodalumab compared to patients continued on ustekinumab (0.6% vs 0.12%).[95] However, overall rates remained small and were not statistically significant between groups.

Table 8. Common adverse effects of brodalumab (with >1% incidence compared to placebo) during phase 3 clinical trials with treatment duration of 12 weeks.[10]

Adverse Effect	Placebo (n=879)	Brodalumab 210 mg q 2 weeks (n=1496)	Ustekinumab (n=613)
Arthralgia	29 (3.3)	71 (4.7)	15 (2.4)
Fatigue	10 (1.1)	39 (2.6)	16 (2.6)
Diarrhea	10 (1.1)	33 (2.2)	5 (0.8)
Oropharyngeal pain	10 (1.1)	31 (2.1)	8 (1.3)
Myalgia	3 (0.3)	26 (1.7)	4 (0.7)

Similar to other biologic treatments for plaque psoriasis, labeling for brodalumab includes warnings for increased risk of serious infection, reactivation of latent tuberculosis, and concomitant use of live vaccines. Overall, trials were not powered to determine differences in infection rates and statistical significance between groups was not evaluated. However, rates of infections during clinical trials were slightly more common in patients receiving brodalumab compared to placebo (25.4% vs. 23.4%).[10] Rates of serious infections and serious fungal infections were also more frequent in patients treated with brodalumab compared to placebo (0.5% vs. 0.2% and 2.4% vs 0.9%, respectively).[10] Upon comparison to ustekinumab, rates of infection and serious infection were similar though trials were not powered to determine differences in outcomes.[10] Decreases in absolute neutrophil count were observed, leading to treatment discontinuation in 2 patients.[95] Tuberculosis testing and treatment of active tuberculosis infection is recommended before initiation of brodalumab. Administration of live vaccines

are not recommended for patients receiving brodalumab. In addition, brodalumab is contraindicated patients with a history of Crohn's disease. In early clinical trials, use of brodalumab lead to exacerbation of Crohn's disease and treatment discontinuation for at least 1 patient.[10] Patients with Crohn's disease were excluded from subsequent phase 3 clinical trials.

Labeling for brodalumab also includes warnings for suicidal ideation and behavior.[10] This does not appear to be a class effect although similar findings were reported in trials with ixekizumab in the treatment of PsO and RA.[94] During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides.[10] Of these patients, 8 had a history of suicidality or depression.[10] No cause-effect relationship was established and epidemiological studies indicate that PsO may be associated with depression.[94] However, upon identification of this safety issue, protocols were modified to exclude patients with a history of severe depression, suicidality or major psychiatric disorder and to screen prospectively for neuropsychiatric events. A total of 57 patients were discontinued from the maintenance phase or open-label extension studies following implementation of prospective screening.[95] FDA analysis indicated neuropsychiatric events were likely underreported during these clinical trials as the incidence of suicidal ideation increased significantly upon implementation of prospective screening.[95] In active controlled studies through 52 weeks, overall incidence of suicidal ideation or behavior in patients receiving brodalumab was 0.17% (95% CI 0.07 to 0.36%, n=7) compared to patients who continued treatment with ustekinumab (0.49%; n=3) or placebo (0%).[95] The incidence of depression, anxiety, or impulsivity was similar between groups.[95] Upon comparison to rate of suicide in clinical trials for other biologics, the relative risk of suicide with brodalumab was approximately 3 times higher than other biologic agents (58 vs. 14 suicides/100,000 patient-years).[95] Because of the retrospective nature and limitations associated with the pooled data analyses, the exact incidence of neuropsychiatric adverse events including depression and suicidal ideation remains unclear.[95]

In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Providers, patients, and pharmacies must be certified through the Siliq™ REMS program.[10] The program ensures both prescribers and patients are aware of the increased risk for suicide associated with brodalumab use. In addition, due to increased risk for these serious adverse effects, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.[10] Post-marketing requirements include studies to determine safety and efficacy in children and adolescents with severe plaque psoriasis, safety outcomes in pregnancy, and long-term safety of brodalumab compared to other therapies. Particular long-term safety outcomes of interest include incidence of malignancy, opportunistic infections, and neutropenia.

Table 9. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	IL-17 receptor antagonist
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 8.9 liters
Elimination	Degraded into small peptides in a manner similar to endogenous IgG
Half-Life	Unknown
Metabolism	Unknown

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:

1) Functional improvement and health-related quality of life
2) Symptom improvement (i.e. redness, itch, scaling, cracking, or pain)
3) Remission rates
4) Serious adverse events (i.e. infection, suicide, Crohn's disease)
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage of patients with ≥75% improvement in the Psoriasis Area and Severity Index score (PASI 75) at week 12
2) Static physicians' global assessment (sPGA) score of 0 or 1 at week 12
3) Percent of patients with 100% improvement in the PASI (PASI 100) at week 12

Table 10. Comparative Evidence Table for Brodalumab

Ref./Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Papp AK, et al.[38] AMAGINE-1 DB, PC, MC, RCT Phase 3	1.Brodalumab 210 mg (B210) SC x12 weeks 2.Brodalumab 140 mg (B140) SC x12 weeks 3.Placebo x 12 weeks Randomized 1:1:1 Injections given at baseline, week 1, week 2 and every 2 weeks thereafter. After 12 weeks, patients were re-randomized to brodalumab or placebo for up to 52 weeks with retreatment if sPGA>2.	<u>Demographics</u>: - Mean age: 46 yr - 73% Male - 91% White - Psoriatic arthritis: 27% - Disease duration: 20 yr - Prior biologic treatment: 46% - Mean PASI: 19.7 - sPGA of 3: 55% - sPGA of 4: 39% - Mean PSI: 19.2 - Mean affected BSA: 27% <u>Inclusion Criteria</u>: - Age 18-75 years - Plaque psoriasis≥6 months - Affected BSA≥10% - PASI≥12 and sPGA≥3 - Negative Tb test <u>Exclusion Criteria</u>: - Current infection, Tb, HBV, HCV, HIV, or h/o serious infection within 8 weeks - H/o Crohn's disease, MI or unstable angina within 1 yr, malignancy within 5 yr - Clinically significant, uncontrolled disease - Abnormal LFTs, WBC, ANC - Other skin conditions or use of topical steroids	<u>ITT</u>: 1. 222 2. 219 3. 220 <u>Attrition (at 12 weeks)</u>: 1. 10 (4%) 2. 7 (3%) 3. 11 (5%)	<u>Primary Endpoints</u>: (at 12 weeks) Percent of patients with sPGA of 0-1 1. 168 (75.7%) 2. 118 (53.9%) 3. 3 (1.4%) p<0.001 for both vs. PBO (RR & CI NR) Percent of patients with PASI 75: 1. 185 (83.3%) 2. 132 (60.3%) 3. 6 (2.7%) p<0.001 for both vs. PBO (RR & CI NR) <u>Secondary Endpoints</u>: (at 12 weeks) Percent of patients with PASI 100 and sPGA of 0: 1. 93 (41.9%) 2. 51 (23.3%) 3. 1 (0.5%) p<0.001 for both vs. PBO (RR & CI NR) PSI≤8 with no items >1 (range 0-32) 1. 135 (60.8%) 2. 116 (53.0%) 3. 9 (4.1%) p<0.001 for both vs. PBO (RR & CI NR)	74%/2 52%/2 81%/2 58%/2 41%/3 23%/5 57%/2 49%/2	Assessed at 12 weeks <u>Serious AE</u>: 1. 4 (1.8%) 2. 6 (2.7%) 3. 3 (1.4%) <u>DC due to AE:</u> 1. 3 (1.4%) 2. 4 (1.8%) 3. 2 (0.9%) <u>Serious Infections:</u> 1. 0 (0%) 2. 2 (0.9%) 3. 1 (0.5%) <u>Injection site reaction:</u> 1. 0 (0%) 2. 3 (1.4%) 3. 1 (0.5%) p-values NR; unable to determine statistical differences	NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias</u>: Low. Randomized via IVR system; stratified by total body weight, prior biological use & location. Baseline characteristics balanced. <u>Performance Bias</u>: High. Patients and providers blinded but specific methods were unclear. Unblinding may occur due to large differences in efficacy between treatment groups. Use of subjective outcomes increases risk of bias. <u>Detection Bias</u>: High. Unblinding may occur due to large differences in efficacy between treatment groups. P-values adjusted for multiplicity using sequential testing. <u>Attrition Bias</u>: Low. Attrition similar between groups. Missing data was classified as a non-response giving a conservative estimate of effect. <u>Reporting Bias</u>: High. CI were NR for outcomes giving uncertain estimate of precision. Data analysts for outcomes were not blinded. Funded by the manufacturer who was involved in study design, analysis, and publication. Applicability: <u>Patient</u>: Broad exclusion criteria limits applicability to patients with other significant uncontrolled comorbid conditions or in patients with active disease (flares). <u>Intervention</u>: Dose-response with B140 and B210. <u>Comparator</u>: Placebo suitable to assess efficacy <u>Outcomes</u>: Use of multiple symptom scales with consistent direction and magnitude of effect. <u>Setting</u>: 73 centers in the USA, Canada, and Europe. Proportion from the USA was NR.

2. Lebwohl MB, et al.[96] AMAGINE-2 DB, PC, AC, MC, RCT Phase 3	1. B210 SC for 12 weeks 2. B140 SC for 12 weeks 3. Ustekinumab SC dosed at 45 mg for ≤100 kg or 90 mg for >100 kg given at baseline, week 4, and every 12 weeks thereafter 4. Placebo 2:2:1:1 B210 and B140 given at baseline, week 1, week 2, and every 2 weeks thereafter. Maintenance phase from 12 to 52 weeks, patients continued to receive USTEKINUMAB or were randomized to B210 every 2 weeks or B140 every 2, 4, or 8 weeks.	Demographics: - Mean age: 45 yr - Male: 69% - White: 90% - Prior systemic therapy: 76% - Prior biologic therapy: 29% - Psoriatic arthritis: 19% - Mean affected BSA: 27% - Disease duration: 19 yr - Mean PASI: 20.3 - Mean PSI: 18.8 - sPGA of 3 (moderate): 54% - sPGA of 4 (severe): 39% Key Inclusion Criteria: - Age 18-75 yr - Stable moderate to severe plaque psoriasis for ≥6 months - Affected BSA≥10% - PASI≥12 and sPGA≥3 - Negative Tb screening Key Exclusion Criteria: - See AMAGINE-1 - Concomitant psoriasis treatment (28 day washout period required for topical or systemic therapies, 12 weeks for biologic therapy), recent administration of live vaccinations - Patients with h/o prior anti-IL-17 biologic therapy - Other forms of psoriasis or skin conditions	ITT: 1. 612 2. 610 3. 300 4. 309 Attrition at 12 weeks: 1. 15 (3%) 2. 22 (4%) 3. 9 (3%) 4. 9 (3%)	Primary Endpoints: (at 12 weeks) Percent of patients with PASI 75: 1. 528 (86%) 3. 210 (70%) 2. 406 (67%) 4. 25 (8%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p=0.08 B140 vs. AC: RR & CI NR; p=0.33 Percent of patients with sPGA of 0-1 1. 481 (79%) 3. 183 (61%) 2. 354 (58%) 4. 12 (4%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.49 Percent of patients with PASI 100: 1. 272 (44%) 3. 65 (22%) 2. 157 (26%) 4. 2 (1%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.08 Secondary Endpoints: (at 12 weeks) PSI≤8 with no items >1 (range 0-32) 1. 414 (68%) 2. 134 (51%) 3. 166 (55%) 4. 21 (7%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR, CI & p-value NR B140 vs. AC: RR, CI & p-value NR Percent of patients with sPGA of 0: 1. 274 (45%) 2. 157 (26%) 3. 65 (22%) 4. 2 (1%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.17	 78%/2 59%/2 NA NA 75%/2 54%/2 18%/6 NA 43%/3 25%/4 22%/6 NA 61%/2 44%/3 NA NA 44%/3 25%/4 22%/6 NA	Assessed at 12 weeks Serious AE: 1.6 (1.0%) 2. 13 (2%) 3. 4 (1.3%) 4. 8 (2.6%) DC due to AE: 1.6 (1%) 2. 7 (1.2%) 3. 4 (1.3%) 4. 1 (0.3%) Serious infection: 1.2 (0.3%) 2. 2 (0.3%) 3. 0 (0%) 4. 1 (0.3%) Injection Site Reactions 1.9 (1.5%) 2. 9 (1.5%) 3. 2 (0.7%) 4. 3 (1.0%) Depression 1. 2 (0.3%) 2. 4 (0.7%) 3. 2 (0.7%) 4. 1 (0.3%) p-values NR; unable to determine statistical significance in safety outcomes	 NA NA NA NA NA	Risk of Bias (low/high/unclear): Selection Bias: Low. Randomization and allocation concealment via IVR system. Patients were stratified based on weight, geographic region and prior biologic use. Baseline characteristics were balanced. Performance Bias: High. Patients and providers blinded with use of double-blind, double-dummy injections. Blinding methods maintained through week 52, though unblinding may occur due to large differences in efficacy between brodalumab and placebo. Detection Bias: High. Assessors for cardiovascular events were blinded. Use of subjective outcomes increases risk of bias. Unblinding may occur due to large differences in efficacy between treatment groups. Attrition Bias: Low. Attrition similar between groups and missing data were imputed as non-responders giving a more conservative estimate of effect. ITT analysis conducted. Multiplicity addressed with use of sequential testing for multiple endpoints. Reporting Bias: High. Amgen, the manufacturer of brodalumab, provided funding, collected data, conducted data analyses, and was involved in writing the manuscript. CI were NR for outcomes giving uncertain estimate of precision. Applicability: Patient: Broad exclusion criteria limits applicability to patients with other significant uncontrolled comorbid conditions or in patients with active disease (flares). Very few patients had very severe disease. Intervention: Dose-response with B140 and B210 Comparator: Placebo appropriate to determine effectiveness. Weight-based dosing of ustekinumab was appropriate. Outcomes: Compared to active control B210 was only significantly improved for outcome of PASI 100 not PASI 75. Setting: 142 sites worldwide from August 2012 to September 2014. Proportion of patients in the United States was NR.

3. Lebwohl MB, et al.[96] AMAGINE-3 DB, PC, AC, MC, RCT Phase 3	1. B210 SC at baseline, week 1, week 2 and every 2 weeks thereafter for 12 weeks. 2. B140 SC at baseline, week 1, week 2 and every 2 weeks thereafter for 12 weeks 3. USTEKINUMAB SC dosed at 45 mg for ≤100 kg or 90 mg for >100 kg given at baseline, week 4, and every 12 weeks thereafter 4. Placebo 2:2:1:1 After 12 weeks, patients were randomized to a maintenance phase through week 52 in which patients continued to receive USTEKINUMAB or received brodalumab 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks.	<u>Demographics</u>: - Mean age: 45 yr - Male: 68% - White: 91% - Prior systemic therapy: 68% - Prior biologic therapy: 25% - Psoriatic arthritis: 20% - Mean affected BSA: 28% - Disease duration: 18 yr - Mean PASI: 20.2 - Mean PSI: 18.5 - sPGA of 3 (moderate): 62% - sPGA of 4 (severe): 34% <u>Key Inclusion Criteria</u>: See AMAGINE-2 <u>Key Exclusion Criteria</u>: See AMAGINE-2	<u>ITT</u>: 1. 624 2. 629 3. 313 4. 315 <u>Attrition at week 12</u>: 1. 16 (3%) 2. 25 (4%) 3. 14 (4%) 4. 10 (3%)	<u>Primary Endpoints:</u> (at 12 weeks) Percent of patients with PASI 75: 1. 531 (85%) 2. 435 (69%) 3. 217 (69%) 4. 19 (6%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p=0.007 B140 vs. AC: RR & CI NR; p=0.95 Percent of patients with sPGA of 0-1: 1. 497 (80%) 2. 337 (60%) 3. 179 (57%) 4. 13 (4%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.44 Percent of patients with PASI 100: 1. 229 (37%) 2. 170 (27%) 3. 58 (19%) 4. 1 (0.3%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.007 <u>Secondary Endpoints</u>: (at 12 weeks) Percent of patients with sPGA of 0: - Same results as PASI 100 Percent of patients with total PSI≤8 with no single items >1 (range 0-32) 1. 382 (61%) 2. 336 (53%) 3. 162 (52%) 4. 20 (6%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR, CI & p-value NR B140 vs. AC: RR, CI & p-value NR	 79%/2 63%/2 16%/7 NA 76%/2 56%/2 23%/5 NA 37%/3 27%/4 18%/6 8%/13 See PASI 100 55%/2 47%/3 NA NA	Assessed at 12 weeks <u>Serious AE:</u> 1. 9 (1.4%) 2. 10 (1.6%) 3. 2 (0.6%) 4. 3 (1.0%) <u>DC due to AE</u>: 1. 7 (1.1%) 2. 5 (0.8%) 3. 2 (0.6%) 4. 3 (1.0%) <u>Serious infection</u>: 1.4 (0.6%) 2. 3 (0.5%) 3. 2 (0.6%) 4. 1 (0.3%) <u>Injection Site Reactions</u> 1.9 (1.4%) 2. 11 (2%) 3. 10 (3%) 4. 6 (1.9%) <u>Depression</u> 1. 2 (0.3%) 2. 4 (0.7%) 3. 1 (0.3%) 4. 2 (0.6%) p-values NR; unable to determine statistical significance in safety outcomes	 NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias</u>: See AMAGINE-2. <u>Performance Bias</u>: See AMAGINE-2. <u>Detection Bias</u>: See AMAGINE-2. <u>Attrition Bias</u>: See AMAGINE-2. <u>Reporting Bias</u>: See AMAGINE-2. Applicability: <u>Patient</u>: See AMAGINE-2. <u>Intervention</u>: Dose-response with B140 and B210 <u>Comparator</u>: Placebo appropriate to determine effectiveness. Weight-based dosing of ustekinumab appropriate. <u>Outcomes</u>: Consistent efficacy response across all scales used (PASI, sPGA, PSI). <u>Setting</u>: See AMAGINE-2.

Abbreviations : AC = active comparator; AE = adverse event; ANC = absolute neutrophil count; ARI = absolute risk increase; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; DC = discontinuation; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; H/o = history of; ITT = intention to treat; IVR = interactive voice response; LFTs = liver function tests; MC = multicenter; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PASI = Psoriasis Area and Severity Index; PBO = placebo; PC = placebo-controlled; PP = per protocol; PSI = psoriasis symptom inventory; RR = relative risk; RD = risk difference; SC = subcutaneous; SD = standard deviation; sPGA = static physician's global assessment; Tb = tuberculosis; WBC = white blood cells; yr = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	PDL
ADALIMUMAB	HUMIRA PEN	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA PEN CROHN-UC-HS STARTER	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA PEN PSORIASIS-UVEITIS	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	Y
ADALIMUMAB	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	Y
ETANERCEPT	ENBREL	PEN INJCTR	Y
ETANERCEPT	ENBREL	SYRINGE	Y
ETANERCEPT	ENBREL	SYRINGE	Y
ETANERCEPT	ENBREL	VIAL	Y
ABATACEPT	ORENCIA CLICKJECT	AUTO INJCT	N
ABATACEPT	ORENCIA	SYRINGE	N
ABATACEPT/MALTOSE	ORENCIA	VIAL	N
ANAKINRA	KINERET	SYRINGE	N
APREMILAST	OTEZLA	TAB DS PK	N
APREMILAST	OTEZLA	TABLET	N
APREMILAST	OTEZLA	TABLET	N
BRODALUMAB	SILIQ	SYRINGE	N
CANAKINUMAB/PF	ILARIS	VIAL	N
CANAKINUMAB/PF	ILARIS	VIAL	N
CERTOLIZUMAB PEGOL	CIMZIA	KIT	N
CERTOLIZUMAB PEGOL	CIMZIA	SYRINGEKIT	N
GOLIMUMAB	SIMPONI ARIA	VIAL	N
GOLIMUMAB	SIMPONI	PEN INJCTR	N
GOLIMUMAB	SIMPONI	SYRINGE	N
INFLIXIMAB	REMICADE	VIAL	N
INFLIXIMAB-DYYB	INFLECTRA	VIAL	N
IXEKIZUMAB	TALTZ AUTOINJECTOR	AUTO INJCT	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	N
IXEKIZUMAB	TALTZ SYRINGE	SYRINGE	N
IXEKIZUMAB	TALTZ SYRINGE (2 PACK)	SYRINGE	N
IXEKIZUMAB	TALTZ SYRINGE (3 PACK)	SYRINGE	N
NATALIZUMAB	TYSABRI	VIAL	N

RITUXIMAB	RITUXAN	VIAL	N
SECUKINUMAB	COSENTYX PEN	PEN INJCTR	N
SECUKINUMAB	COSENTYX PEN (2 PENS)	PEN INJCTR	N
SECUKINUMAB	COSENTYX (2 SYRINGES)	SYRINGE	N
SECUKINUMAB	COSENTYX SYRINGE	SYRINGE	N
TOCILIZUMAB	ACTEMRA	VIAL	N
TOCILIZUMAB	ACTEMRA	SYRINGE	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	N
TOFACITINIB CITRATE	XELJANZ	TABLET	N
USTEKINUMAB	STELARA	VIAL	N
USTEKINUMAB	STELARA	SYRINGE	N
USTEKINUMAB	STELARA	VIAL	N
VEDOLIZUMAB	ENTYVIO	VIAL	N

Appendix 2: Medline Search Strategy

[Example]

Ovid MEDLINE(R) without Revisions 1996 to May Week 1 2017

1 Adalimumab/	*3704*
2 Etanercept/	*4895*
3 tocilizumab.mp.	*1425*
4 Abatacept/	*2292*
5 Infliximab/	*8285*
6 Rituximab/	*10713*
7 golimumab.mp.	*557*
8 apremilast.mp.	*157*
9 tofacitinib.mp.	*406*
10 certolizumab.mp.	*671*
11 Certolizumab Pegol/	*396*
12 secukinumab.mp.	*191*
13 Abatacept/	*2292*
14 ixekizumab.mp.	*96*
15 Ustekinumab/	*515*
16 Natalizumab/	*1158*
17 vedolizumab.mp.	*160*
18 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	*29525*
19 Arthritis, Rheumatoid/	*44049*
20 Spondylitis, Ankylosing/	*6249*
21 Arthritis, Juvenile/	*4789*
22 Arthritis, Psoriatic/	*4057*
23 Crohn Disease/	*20816*
24 Antibodies, Monoclonal/ or Psoriasis/ or Anti-Inflammatory Agents/ or Immunosuppressive Agents/ or Dermatologic Agents/	*229148*
25 Colitis, Ulcerative/	*15880*
26 19 or 20 or 21 or 22 or 23 or 24 or 25	*301643*
27 18 and 26	*22371*
28 limit 27 to (english language and full text and yr="2015 - 2017" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	*198*

Appendix 3: Prescribing Information Highlights

SILIQ™ (brodalumab) injection, for subcutaneous use

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SILIQ™ (brodalumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SUICIDAL IDEATION AND BEHAVIOR

See full prescribing information for complete boxed warning.

- **Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)**
- **Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. (5.1)**
- **Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. (5.1)**
- **Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. (5.1)**
- **SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)**

INDICATIONS AND USAGE

SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (1)

DOSAGE AND ADMINISTRATION

- Administer 210 mg of SILIQ by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- Crohn's disease (4)

WARNINGS AND PRECAUTIONS

- Infections: Serious infections have occurred. Consider the risks and benefits prior to initiating SILIQ in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue SILIQ until the infection resolves. (5.3)
- Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment with SILIQ. (5.4)
- Crohn's Disease: Crohn's disease occurred during clinical trials. Discontinue SILIQ if patient develops Crohn's disease while taking SILIQ. (5.5)
- Immunizations: Avoid using live vaccines concurrently with SILIQ. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥1%) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017

Biologics for Autoimmune Diseases

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

All biologics except for biologics approved by the FDA for the following indications:

- Non-Hodgkin Lymphoma
- Chronic Lymphocytic Leukemia
- Juvenile Idiopathic Arthritis
- Multiple Sclerosis
- Non-infectious posterior uveitis
- Familial Cold Autoinflammatory Syndrome
- Granulomatosis with Polyangitis
- Muckel-Wells Syndrome
- Neonatal Onset Multi-Systemic Inflammatory Disease
- Tumor Necrosis Factor Receptor Associated Periodic Syndrome
- Hyperimmunoglobulin D Syndrome
- Mevalonate Kinase Deficiency
- Familial Mediterranean Fever

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. Approved Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infec-tious)	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			
Adalimumab (HUMIRA)	≥18 yo	≥6 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Anakinra (KINERET)						≥18 yo			NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo				
Brodalumab (SILIQ)					≥18 yo				
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥18 yo			
Etanercept (ENBREL)	≥18 yo		≥2 yo	≥4 yo	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo (SIMPONI ARIA is only FDA approved for RA)	≥18 yo		
Infliximab (REMICADE)	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Infliximab-dyyb (INFLECTRA)	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥18 yo		
Ixekizumab (TALTZ)				≥18 yo					
Natalizumab (TYSABRI)		≥18 yo							MS ≥18 yo
Rituximab (RITUXAN)						≥18 yo			CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo

Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			
Sarilumab (KEVZARA)						≥18 yo			
Tofacitinib (XELJANZ)						≥18 yo			
Ustekinumab (STELARA)		≥ 18 yo		≥18 yo	≥18 yo				
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: CLL = Chronic Lymphocytic Leukemia; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MS = Multiple Sclerosis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to # 21	**No:** Go to #4
~~3.~~4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5

Approval Criteria		
5. Is the prescription for rituximab for non-Hodgkin Lymphoma) or Chronic Lymphocytic Leukemia? OR Is the prescription for natalizumab, prescribed for the management of relapsing multiple sclerosis? OR Is the diagnosis Non-infectious Posterior Uveitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #6
~~4.~~6. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	Yes: Go to #7	No: Go to #8
~~5.~~7. Has the patient failed to respond to adalimumab or etanercept after a trial of at least 3 months?	Yes: Document therapy with dates: _____ Approve for up to 6 months	No: Pass to RPh. Deny; medical appropriateness.
~~6.~~8. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #9	**No**: Go to #11

Approval Criteria		
~~7.~~9. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; not funded by the OHP.
~~8.~~10. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • Had treatment failure with at least one biologic agent either adalimumab or etanercept for at least 3 months?	**Yes**: Document each therapy with dates: _____ Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
~~9.~~11. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #12	**No:** Go to #15

Approval Criteria		
~~10.~~12. Has the patient failed to respond to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: adalimumab or etanercept for at least 3 months?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
~~11.~~13. Is the request for tofacitinib?	**Yes:** Go to #14	**No:** Approve for up to 6 months
~~12.~~14. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months
~~13.~~15. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #16	**No:** Go to #17

Approval Criteria		
~~14.~~16. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • For Crohn's Disease patients only: has the patient tried and failed a 3 month trial of adalimumab?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
~~15.~~17. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment	**No:** Go to #18
~~16.~~18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #19	**No:** Go to #20
~~17.~~19. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
20. Is the diagnosis Juvenile Idiopathic Arthritis or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
21. Has the patient's condition improved as assessed for each diagnosis by the appropriate outcome: • For Ankylosing Spondylitis: Reduction in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to 50% of the pretreatment value, OR Improvement in Ankylosing Spondylitis Disease Activity Score (ASDAS) > 1.0 points on 0-10 scale • For Psoriasis: 50-75% reduction in Psoriasis Area and Severity Index (PASI) from pretreatment value OR 5 point reduction in Dermatology Quality of Life (DQLI) score • Rheumatoid Arthritis: Reduction in Disease Activity Score (DAS-28) by 0.6 points from pretreatment value, OR 50-70% reduction in American College of Rheumatology (ACR) score from pretreatment values.	Document : 1. Baseline Assessment_____ 2. 6 month post treatment score_____ Yes: Approve for 6 months	No: Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *7/17 (DM); 11/16 (AG); 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 1/1/17; 9/27/14; 2/21/13*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Class Update: Antidiabetic Agents (excluding insulins)

Month/Year of Review: July 2017
End date of literature search: May 22, 2017
Last Review: September 2016
PDL Classes: DPP-4 Inhibitors; GLP-1 Receptor Agonists; Oral Hypoglycemics (sulfonylureas and meglitinides); SGLT-2 Inhibitors; Thiazolidinediones; Miscellaneous Antidiabetic Agents

Current Status of PDL Class:
- See Appendix 2

Purpose of Review:
To evaluate new evidence for each non-insulin antidiabetic drug class on the Preferred Drug List (PDL) and, if appropriate, update current recommendations for placement of specific agents within these drug classes on the Oregon Health Plan (OHP) PDL and current clinical prior authorization (PA) criteria.

Research Questions:
1. Is there any new comparative evidence for non-insulin diabetes treatments on surrogate efficacy outcomes (e.g., hemoglobin A1C [A1C] less than 7%) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for non-insulin diabetes treatments on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, etc.)?
3. Are there subpopulations of patients with diabetes mellitus for which specific therapies may be more effective or associated with less harm?

Conclusions:
There were 3 systematic reviews with meta-analyses[1–3], 6 new clinical practice guidelines (American Diabetes Association [ADA], American College of Physicians [ACP], 3 from the National Institute for Health and Care Excellence [NICE], and one from the American Association of Clinical Endocrinologists/American College of Endocrinology [AACE/ACE])[4–9], 4 new safety alerts[10–13], 4 new drug formulations[14–17] and 3 new randomized controlled studies (RCTs)[18–21] that provide clinically meaningful new evidence for these drugs. The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed. Several systematic reviews and meta-analyses were not included due to poor quality or because the evidence available for the analysis was of poor quality.[22-32]

EFFICACY OUTCOMES

- *Mortality:* Head-to-head RCTs are often underpowered to detect differences in mortality. Many RCTs that have evaluated clinically meaningful effectiveness outcomes (e.g., mortality, macrovascular and microvascular outcomes) lack long-term data, do not report cardiovascular (CV) mortality, have low incidence of mortality overall, and have low or insufficient quality of evidence for these outcomes. Caution is advised in drawing strong conclusions on these outcomes subject to these limitations. **Table 1** describes evidence related to A1C lowering, CV events and harms.
    - There is low quality evidence that there are no differences in CV outcomes or all-cause mortality between antidiabetic treatments for patients with type 2 diabetes mellitus (T2DM) based on mean trial duration of 6 months.[2]
    - There is moderate evidence in patients with T2DM that metformin is associated with less CV-related mortality than sulfonylureas (SU) (absolute difference [AD] -2.9% to -0.1%; 2 RCTs).[1]
    - There is moderate evidence liraglutide lowers the risk for the composite endpoint of CV-related mortality, non-fatal myocardial infarction (MI), or non-fatal stroke compared to placebo at 36 months (Absolute risk reduction [ARR]= 1.9%; number needed to treat [NNT]= 53). Liraglutide reduced the risk of CV-related mortality (ARR= 1.3%; NNT of 77) and all-cause mortality (ARR of 1.4%; NNT 71) versus placebo over 3.5 years.[18] The ADA guideline recommends liraglutide be considered in T2DM patients with established atherosclerotic disease.[5]
    - There is moderate evidence from a double-blind, multi-center randomized controlled trial, in patients with CV disease or at high risk for CV disease, that canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo by an ARR of 1.3% (NNT 77) over 3.6 years.[21] None of the component endpoints were statistically different from placebo. There was a higher risk of amputations in patients treated with canagliflozin compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75).
- *Hemoglobin A1c:*
    - There is high quality evidence to recommend metformin first for patients with T2DM requiring antidiabetic treatment to meet glucose targets. [4,5,32]
    - There is moderate to high level of evidence, based on two high quality systematic reviews and meta-analyses, that A1C lowering is similar between monotherapy antidiabetic therapies, except for DPP-4 inhibitors which were found to have less glucose lowering than metformin[1,2] or SU[1].

SAFETY OUTCOMES

- *Hypoglycemia:* There is high quality evidence that the risk of hypoglycemia is higher with SU therapy than metformin, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 RAs.[1,2]
    - Use of SU was associated with a higher incidence of severe hypoglycemia compared to metformin (absolute difference [AD] 0.8% to 14%) and higher rates of mild, moderate or total hyperglycemia when compared to GLP-1 RAs and DPP-4 inhibitors based on moderate evidence (AD 6% to 21% ; $p<0.05$).[1]
- *Heart Failure:* An update from the U.S. Food and Drug Administration (FDA) reports saxagliptin and alogliptin may increase the risk of heart failure (HF), especially in patients with preexisting heart or kidney disease.[12]
- *Weight:* There is moderate to high evidence that metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with weight loss and SUs and thiazolidinediones (TZDs) are associated with weight gain.[1,2]
    - In monotherapy comparisons, metformin was associated with a mean difference of 1.3 kg weight loss compared to a DPP-4 inhibitor ($p<0.05$). Use of a TZD was associated with a mean weight gain of 1.2 kg more than with a SU ($p<0.05$). Use of a SU was associated with a mean weight gain of 2.3 kg more than with a GLP-1 RA ($p<0.05$). Table 1 gives an overview of relative effect of each antidiabetic class on weight when compared to placebo.

- *Bladder Cancer:* The FDA has added a warning to pioglitazone labeling that it may be associated with increased risk for bladder cancer, although the risk is not fully illucidated.[10] However, data analysis shows conflicting results suggested with hazard ratios (HR) that ranged from 1.0 (95% CI, 0.59 to 1.72) to 1.63 (95% CI, 1.22 to 2.19).
- *Amputations:* An FDA black boxed warning has been added to canagliflozin labeling due to the increased risk of amputations.[11] Amputation rates were 5.9 out of every 1,000 patients treated for canagliflozin compared to 2.8 for placebo out of every 1,000 patients treated based on the CANVAS study. A second study, CANVAS-R, found the risk to be 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 patients treated with placebo. The mechanism is unknown and the applicability of this risk to the entire class is still being determined.

PLACE IN THERAPY

- Moderate quality evidence demonstrates that adding a second antidiabetic therapy to metformin results in a similar A1C lowering of 0.9 -1.1%. A SU, DPP-4 inhibitor, or pioglitazone are recommended as second-line agents in combination with metformin by NICE if monotherapy with metformin fails to get patients to their treatment goal.[8] Triple therapy regimens recommended by NICE are: 1) metformin, DPP-4 inhibitor, and a SU; 2) metformin, pioglitazone and a SU 3); metformin, pioglitazone or SU, and an SGLT-2 inhibitor; or 4) insulin-based treatment.[8] GLP-1 RAs are recommended by NICE if patients on metformin and 2 other treatments, fail to meet glucose lowering targets and meet additional criteria as described below.
- Dual therapy treatment options recommended by the ADA, in combination with metformin, are: SU, thiazolidinedione (TZD), DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA or basal insulin.[5] ACP recommends a SU, TZD, SGT-2 inhibitor, or a DPP-4 inhibitor if a second oral agent is required in addition to metformin.[4]
- There is high quality evidence from a report by CADTH that SU should be added to metformin in patients with T2DM and without established CV disease that fail to meet glucose lowering targets.[3] Moderate quality evidence recommends the use of empagliflozin for patients with T2DM and a high risk of CV disease.[3]

Table 1. Non-insulin Glucose Lowering Drugs Effectiveness and Harms Comparisons

Drug Class	Relative A1C lowering[33]	Cardiovascular Data	Safety Warnings	Effect on Weight[1,5]
Biguanides • Metformin	1% to 1.5%	• UKPDS found that metformin may reduce the risk of CV mortality[34]	• Very small risk of lactic acidosis in patients with poor renal function	• Neutral/ loss
Sulfonylureas (2nd generation) • Glyburide • Glipizide • Glimepiride	1.0% to 1.5%	• No evidence of CV risk reduction	• Risk of hypoglycemia is higher than other oral antidiabetic treatments[1]	• Gain
Thiazolidinediones • Pioglitazone • Rosiglitazone	1.0% to 1.5%	• Use in patients with pre-diabetes and history of stroke or TIA was found to decrease subsequent stroke or MI (ARR 2.8%/NNT 36) compared to placebo over 4.8 years[20]	• Pioglitazone may increase the risk of bladder cancer compared to placebo[10] • TZDs increase the risk of HF exacerbations • TZDs increase the risk of bone fractures	• Gain

		• No CV morbidity or mortality benefit when rosiglitazone was added to metformin and SU[35] • No benefit or harm on CV endpoints with the use pioglitazone compared to placebo (HR 0.90; 95% CI, 0.80 to 1.02; p=0.095)[36]		
DPP-4 Inhibitors • Sitagliptin • Saxagliptin • Alogliptin • Linagliptin	0.5% to 1.0%	• Saxagliptin and alogliptin have demonstrated increased risk in HF related hospitalizations. No difference in CV mortality was demonstrated.[37,38] • Sitagliptin was found to provide no benefit or harm to CV endpoints[40] • Linagliptin is still being evaluated	• Saxagliptin and alogliptin have been linked to increased risk of heart failure[12] • DPP-4 inhibitors may increase risk of pancreatitis • DPP-4 inhibitors may increase risk of severe joint pain	• Neutral/ loss
SGLT2 Inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin	0.5% to 1.0%	• Empagliflozin demonstrated a reduction in the composite endpoint of death from CV causes, nonfatal MI and nonfatal stroke when compared to placebo (ARR 6%/NNT 63) over 3.1 years in patients with underlying CV disease.[39] • Canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo by an ARR of 1.3% (NNT 77) over 3.6 years in patients with CV disease or at high risk for CV disease.[21]	• Canagliflozin increases risk for amputations[11] • Canagliflozin and dapagliflozin are associated with acute kidney injury • SGLT2 inhibitors are associated with ketoacidosis and serious urinary tract infections • Canagliflozin may increase the risk of reduced bone mineral density and fracture	• Loss
GLP-1 Receptor Agonists • Exenatide • Exenatide Once-weekly • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	1.0% to 1.5%	• Liraglutide was found to decrease the composite outcome of death from CV causes, nonfatal MI, nonfatal stroke compared to placebo (ARR 1.9%/ NNT 53) over 3.5 years in patients on standard therapy with a history of CV disease or at high risk of CV disease[18] • Lixisenatide demonstrated no benefit or harm when compared to placebo for the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke,	• GLP-1 RA class may increase the risk of pancreatitis • An increased risk of thyroid cell cancers was demonstrated in rodent models	• Loss

		or hospitalization for unstable angina (HR 1.02; 95% CI, 0.89 to 1.17)[41]		
Meglitinides • Repaglinide • Nateglinide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Gain
Alpha-glucosidase Inhibitors • Acarbose • Miglitol	0.5% to 1.0%	• ACE Trial is ongoing	• No major safety warnings	• Neutral
Amylin Mimetics • Pramlintide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Loss

Recommendations:

- New evidence does not require a change to the current policy.
- Add new formulations to existing PA criteria.
- No changes to the PDL are recommended based on the new evidence. Evaluate comparative costs in executive session.

Previous Conclusions

- There is insufficient comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for T2DM
- There is insufficient evidence to compare health outcomes of the newer diabetes medications and combinations.
- There is high quality evidence that monotherapy with either metformin, a TZD or a SU results in similar lowering of A1C based on one systematic review. There is moderate quality evidence that DPP-4 inhibitors lower A1C less than metformin and glimepiride based on two systematic reviews (one for each comparison).
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews. Evidence from a recent systematic review and meta-analysis found glyburide to be associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.
- Moderate quality evidence from one fair and one good quality trial suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Hospitalization rates in patients with heart failure were higher in clinical trials of saxagliptin compared to placebo.
- A systematic review and meta-analysis on SGLT2 inhibitors, including canagliflozin and dapagliflozin, demonstrated A1C lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]). The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90)] and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to7.45]).
- In patients with a history of cardiovascular (CV) disease, there is moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) can decrease risk for CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed

to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99) in patients with high cardiovascular risk. Reduction in risk is primarily driven by a 2.2% reduction in CV death (3.7% vs. 5.9%) and not non-fatal MI or non-fatal stroke.

Previous Recommendations:

- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.
- Prior authorize the GLP-1 agonists and DPP-4 inhibitors to limit use to patients who have tried and failed therapy with metformin and sulfonylureas.
- Prior authorize SGLT-2 inhibitors to limit for patients unable to tolerate or have contraindications to all other therapies proven to be safe and effective (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin).

Background:

Type 2 diabetes mellitus is a prevalent disease affecting an estimated 25.6 million people in the United States, based on 2013 data. In Oregon, it is estimated that 287,000 adults have T2DM, in which 38,000 are estimated to be OHP members.[42] OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[42] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[43] Despite a variety of treatment options, a significant number of patients fail to meet A1C goals; within 3 years of being diagnosed, 50% of patients require combination therapy to control their disease.[44,45] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and the addition of pharmacotherapy for persistent hyperglycemia.[32,33] Guidelines recommend a goal A1C of < 7% for most patients but a range of <6.5% to <8% is reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[5] Classes of non-insulin antidiabetic agents currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT-2 inhibitors, SUs, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines continue to recommend metformin a first line treatment in most patients with T2DM.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. Hemoglobin A1C is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well.[32,33] A clinically relevant change in A1C is considered to be ≥0.3%.[1] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most available antidiabetic treatments to control glucose levels long-term and to compare their impact on microvascular and macrovascular complications. However, in 2008 the Food and Drug Administration (FDA) started requiring that CV risk be evaluated. Evidence has demonstrated an increased risk of HF-related hospital admissions with alogliptin (NNH 167) and saxagliptin (NNH 143).[37,38] For GLP-1 RAs, lixisenatide demonstrated no benefit or harm in patients with a recent acute coronary syndrome (ACS).[41] The results of the liraglutide study is included in this update and also showed CV benefits. There is moderate evidence from one trial that the SGLT-2 inhibitor empagliflozin demonstrated a 1.6% absolute reduction in the composite primary endpoint of CV death, non-fatal MI, or non-fatal stroke compared to placebo (10.5% vs. 12.1%, respectively; NNT 63 over 3.1 years).[39] Available evidence suggests that metformin is likely to reduce the incidence of CV disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS).[46] UKPDS data also shows reduced incidence of microvascular risk with SU therapy and insulin.[34]

Current OHP fee-for-service policy for non-insulin antidiabetic treatment allows for metformin use without restriction which is designated as a preferred drug (Appendix 1). Therapeutic options in the SU and TZD class are also available without restriction. DPP-4 inhibitors and GLP-1 RAs are options after trials of metformin and SU or contraindications to these drugs (Appendix 4). The DPP-4 inhibitor sitagliptin is also a preferred drug but requires that patients meet specific clinical PA criteria. SGLT2 inhibitors are available as last-line therapy as described in the clinical PA criteria.

Utilization:
The majority of non-insulin anti-diabetic treatment costs were for metformin, SU, TZDs, DPP-4 inhibitors, GLP-1 RAs and SGLT2 inhibitors. Ninety-nine percent of prescriptions dispensed were for metformin, SU or TZD. Metformin was associated with the highest utilization accounting for 78% of the prescriptions dispensed and 48% of the costs. GLP-1 RAs prescriptions accounted for 42% of the costs but < 1% of the prescriptions dispensed. SU were found to be associated with 19% of the prescriptions dispensed and 12% of the costs. Two percent of the utilization and costs were for TZD therapy. The cost for SGLT-2 class accounted for 3% of costs but < 1% of prescription volume. DPP-4 inhibitors accounted for < 1% utilization and costs.

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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:

AHRQ – Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes
A systematic review and meta-analysis was performed to determine the comparative effectiveness and safety of antidiabetic treatments used alone or in combination with metformin.[1] Studies were included if they were head-to-head monotherapy comparisons of metformin, TZDs, SU, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs; comparisons to metformin alone with a metformin-based combination; and comparisons of metformin-based combinations where the second medication was one of the monotherapies described above or a basal or premixed insulin. The Jadad scale was used to evaluate the quality of the RCTs and the Downs and Black tool was utilized for non-randomized and observational studies. One-hundred sixteen new studies were included, 81% were RCTs, for a total of 204 studies all together. Funding was provided by Agency for Healthcare Research and Quality (AHRQ) and no authors reported a conflict of interest.

The evidence was graded low or insufficient for all-cause mortality, CV morbidity and microvascular complications. There is insufficient evidence on the study of long-term outcomes.[1]

Cardiovascular mortality: metformin was found to have a lower incidence than SU (moderate evidence).

- Based on evidence from 2 RCTs that found a relative risk of CV mortality of 0.6 to 0.7 favoring metformin over SU, with an absolute difference of 0.1% to 2.9%.[1]

Hemoglobin A1C lowering: reductions were similar across all antidiabetic therapies and metformin-based combinations. The exception was DPP-4 inhibitors which had less lowering compared to metformin and SU (based on moderate to high evidence for all comparisons).[1]

- Analysis of 14 studies found no clinically meaningful difference (≥0.3%) in A1C between antidiabetic therapies.

Body weight: maintenance or reductions were seen with metformin, DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors.[1] Weight was increased with SU, TZDs, and insulin with between group differences of up to 5 kg.

- Results were significant for metformin compared to DPP-4 inhibitors where an analysis of 6 studies found a mean difference of -1.3 kg (95% CI, -1.6 to -1.0 kg; $p<0.05$) favoring metformin (high level of evidence). TZDs caused significantly more weight gain compared to SU by a mean difference of 1.2 kg (95% CI, 0.6 to 1.8 kg; $p < 0.05$) (high level of evidence). SUs increase weight by a mean difference of 2.3 kg (95% CI, 1.2 to 3.3 kg; $p<0.05$) more than GLP-1 RAs based on 4 studies (moderate level of evidence). Comparisons in which meta-analyses were not able to be conducted are presented in **Table 2** below.
- Metformin monotherapy was found to decrease weight by a mean difference of 2.2 kg (95% CI, -2.6 to -1.9 kg; $p<0.05$) when compared to metformin/TZD combination. A mean difference of -3.2 kg (95% CI, -4.6 to -1.6 kg; $p<0.05$) was found between metformin monotherapy and metformin/SU combinations, favoring monotherapy, in patients who weight 90 kg or more based on high strength of evidence. In patients weighing less than 90 kg, metformin monotherapy was associated with a mean difference in weight of -1.2 kg (95% CI, -1.6 to -0.6 kg; $p < 0.05$) based on high strength of evidence from 5 studies.

Table 2. Summary of Moderate to High Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combinations Therapy Where Meta-analyses Could Not Be Conducted for Weight.[1]

Comparison	RCTs (Participants), *n (n)*	Range in Mean Between-Group Differences	Conclusion	Strength of Evidence
SU vs. DPP-4 inhibitors	4 (1659)	0.7 to 1.8 kg	DPP-4 inhibitors favored	Moderate
DPP-4 inhibitors vs. TZD	2 (1475)	−2.3 to −2.5 kg	DPP-4 inhibitors favored	Moderate
GLP-1 receptor agonists vs. TZD	2 (1048)	Both studies: −3.5 kg	GLP-1 receptor agonists favored	Moderate
SGLT-2 inhibitors vs. Met	3 (1903)	−1.3 to −1.4 kg	SGLT-2 inhibitors favored	Moderate
SGLT-2 inhibitor vs. DPP-4 inhibitors	1 (899)	−2.5 to −2.7 kg	SGLT-2 inhibitors favored	Moderate
Met + SGLT-2 inhibitors vs. Met + DPP-4 inhibitors	5 (3423)	−1.8 to −3.6 kg	Met + SGLT-2 inhibitors favored	Moderate
Met + SU vs. Met + premixed or basal insulin	3 (894)	−1.7 to −0.6 kg	Met + SU favored	Moderate
Met + GLP-1 receptor agonists vs. Met + premixed insulin	2 (426)	−1.9 to −5.1 kg	Met + GLP-1 receptor agonists favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; RCT = randomized, controlled trial; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylureas; TZD= thiazolidinedione.

Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. Annals of Internal Medicine. 2016;164(11):740-751. doi:10.7326/M15-2650.

Hypoglycemia: SUs were most often associated with hypoglycemia as monotherapy and in combination therapy regimens (moderate to high evidence).

- In studies that compared metformin to SU, risk for severe hypoglycemia was 0.8% to 14% higher with SU ($p<0.05$). In comparisons of combination therapy, metformin/SU therapy was associated with an increased risk of severe hypoglycemia compared to metformin/DPP-4 inhibitors (OR 0.2; 95% CI, 0.1 to 0.6; $p<0.05$) (moderate evidence). Metformin/SU were also associated with a 1% to 3% increased risk of severe hypoglycemia compared to metformin/SGLT2 inhibitors.
- SU as monotherapy or in combination therapy was associated with a higher rate of mild, moderate, or total hyperglycemia versus GLP-1 RA, DPP-4 inhibitors, and metformin (OR 2.0 to 3.8; $P < 0.05$).

Gastrointestinal Adverse Events: GI adverse events are defined as diarrhea, nausea and vomiting for this endpoint. There was moderate to high strength of evidence that metformin and GLP-1 RAs, as monotherapy and in combination with other antidiabetic treatments, were associated with the highest incidence of adverse GI events.[1] In comparisons between GLP-1 RAs and SU, GLP-1 RAs were associated with a 3% to 9% increased risk of adverse GI events. Combination therapy of metformin/GLP-1 RA had a 0% to 23% higher risk for adverse GI events compared to metformin/DPP-4 inhibitor ($p<0.05$). Metformin/GLP-1 RA combination were also associated with 8% to 19% more adverse GI events than metformin/TZDs ($p<0.05$). No difference was found in the risk of GI adverse events between TZDs and SU and the combination of metformin/SU and metformin/TZD.

Genital Mycotic Infections: There was moderate to high strength of evidence that risk of genital mycotic infections was higher with SGLT2 inhibitors compared to placebo and active treatments. When metformin was compared to metformin/SGLT2 inhibitor, the risk of genital mycotic infections was up to 9.9% higher for the combination therapy (OR 3.0; 95% CI, 1.2 to 7.2 for women and OR 2.7; 95% CI, 0.8 to 9.0 for men). In a comparison between metformin/GLP-1 RA and metformin/SU combinations, there was a 7.1% to 17.4% $P < 0.05$) increase in genital mycotic infections with metformin/SGLT2 ($p<0.05$). In a comparison

between SGLT2s and metformin, SGLT2s were associated with increased risk of genital mycotic infections by -0.04% to 15.7% ($p<0.05$). A comparison between metformin/SGLT2 inhibitor and metformin/DPP-4 inhibitor combinations found a -2.8% to 8.8% increase in genital mycotic infections with metformin/SGLT2.

In summary, the new evidence that was identified since the 2015 AHRQ review supports the current guideline recommendations. Metformin remains the first-line treatment in patients with T2DM who require therapy to reduce glucose levels. The optimal second-line agent to add to metformin to in most patients is not clear and dependent upon patient specific characteristics. With lack of long-term outcomes, practitioners must balance adverse events, costs, comorbidities and administration concerns when choosing a second antidiabetic agent.

Palmer, et al. – Clinical Outcomes and Adverse Events of Glucose-Lowering Drugs

In a systematic review and meta-analysis, the efficacy and safety of drugs used to treat T2DM were compared. Three-hundred and one RCTs that were at least 24 weeks (median 6 months) in duration that compared two individual glucose lowering therapies were included.[2] Classes included in the review were: metformin, SU, DPP-4 inhibitors, GLP-1 RA, SGLT-2 inhibitors, basal insulin, meglitinide, and alpha-glucosidase inhibitors. Insulin therapies of basal-bolus and prandial insulin were included if they were compared to previous drug classes already mentioned, placebo or standard therapy. Monotherapy (n=177 studies), drugs added to metformin (n=109 studies) and drugs added to metformin and a SU (n=29 studies) were identified. Patients included had a baseline A1C of 8.2%-8.4% and mean duration of diabetes of 5.7 years. The Cochrane risk of bias tool was used to determine study quality. Depending on the domain, the risk of bias ranged from 31.9%-93.4%. Trials were excluded (n=1035) on a methodological basis for non-parallel study design and lack of reporting of meta-analysis outcomes. The primary outcome was CV mortality. Secondary outcomes were all-cause mortality, serious adverse events, MI, stroke, change in A1C, treatment failure, hypoglycemia and body weight. Several authors had received funding from industry. Funding for the analysis was provided by the Royal Society of New Zealand.

The incidence of CV and all-cause mortality outcomes between antidiabetic treatment when compared as monotherapy (n=25 studies), dual therapy (with metformin) (n=26 trials) and triple therapy (with metformin and SU) were not statistically significantly different.[2]

Monotherapy Comparisons: No evidence was available for GLP-1 RAs and basal insulin for monotherapy comparisons. All monotherapy antidiabetic treatment comparisons were more effective than placebo with an A1C standard mean difference (SMD) of -0.66% to -1.11%. In metformin comparisons, metformin resulted in lower A1C than alpha-glucosidase inhibitors, DPP-4 inhibitors, SU and TZDs (SMD 0.16% to 0.35%). SGLT-2 inhibitors, basal insulins, GLP-1 RA and meglitinides were not statistically significantly different from metformin. Treatment failure was highest with placebo (11%; 95% CI, 8 to 14%), followed by meglitinides (5%; 95% CI, 1 to 9%) and DPP-4 inhibitors (3%; 95% CI, 1 to 6%).[2] Compared to metformin SGLT2 inhibitors were associated with the lower risk of treatment failure by a difference of -0.3% (95% CI, -4% to 3%), which is unlikely to be clinically significant. The two treatments most commonly associated with hypoglycemia, based on placebo and active treatment comparisons, were basal insulin (AD 10%; 95% CI 0.08% to 20%) and SU (AD 10%; 95% CI, 7% to 13%). When compared to metformin, GLP-1 RAs were associated with the lower body weight with a SMD of -0.28 kg. SU and TZDs were associated with 0.19 kg to 0.24 kg higher body weight than metformin.[2] Differences in body weight were small suggesting the clinical significance is low.

Dual Therapy Comparisons with Metformin: Metformin/DPP-4 inhibitor combination therapy was associated with lower risk of stroke when compared to metformin/SU (AD -0.2%; 95% CI -0.4% to -0.04%).[2] Differences were small and unlikely to be clinically significant. For all other dual combination therapy comparisons with metformin, the outcomes of serious adverse events, MI or stroke were not significantly different. Similar levels of A1C lowering were seen with all dual combination comparisons; however, there was substantial heterogeneity in the comparison making conclusions difficult. In comparisons of dual combination therapy, metformin/SGLT-2 inhibitor therapy was associated with 3% lower rate of treatment failure compared to metformin/SU (95% CI; -6% to -

0.8%).[2] Metformin/alpha-glucosidase inhibitor, followed by metformin/DPP-4 inhibitor, were associated with the highest treatment failure rates compared to other metformin combinations. Hypoglycemia rates were higher with metformin/SU. The difference in risk of hypoglycemia was -4% to -22% lower with other combinations compared to metformin/SU. Metformin combined with a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 RA resulted in a mean weight decrease of -0.58 kg to -1.05 kg when compared to metformin/SU combination therapy.

Triple Combination with Metformin and SU: No differences were found between any comparisons for all-cause mortality or serious adverse event outcomes. There was insufficient evidence for MI and stroke. The combination of metformin/SU plus TZD or basal insulin were associated with greatest A1C reduction. Metformin/SU plus an alpha-glucosidase inhibitor had the least A1C lowering when compared to or metformin/SU plus TZD, GLP-1 RA, or basal insulin.[2] Treatment failure rates were lowest with metformin/SU plus basal insulin and highest with metformin/SU plus DPP-4 inhibitor. A GLP-1 RA added to metformin and SU resulted in the lowest risk of hypoglycemia of all triple therapy studied. The largest difference in hypoglycemia rates were seen when GLP-1 RAs were compared to TZDs combined with metformin and SU which demonstrated a 10% difference between the groups (95% CI, -18 to 2) favoring GLP-1 RAs; however, this was not statistically significant. Changes in body weight were significantly lower for SGLT2 inhibitors (SMD -0.33 kg), which is unlikely to be clinically significant.

In summary, monotherapy comparisons with metformin found DPP-4 inhibitors and alpha-glucosidase inhibitors resulted in 0.33% to 0.35% lower mean A1C values. Compared to metformin, SU and basal insulin had clinically significant increases in hypoglycemia rates. GLP-1 RAs were associated with the least changes in body weight with a mean decrease in body weight of 0.28 kg. For dual therapy comparisons, there is no clear difference in glucose lowering. SU therapy, alone or in combination, is consistently associated with a higher risk of hypoglycemia. TZDs were consistently associated with the most weight gain. There were no significant correlations between the degree of A1C lowering, hypoglycemia and body weight and characteristics at baseline based on a network meta-regression analyses. Cardiovascular and mortality outcomes remain imprecise, primarily due to short trial durations, lack of reporting CV mortality and low incidence of mortality in studies.

<u>CADTH – New Drugs for Type 2 Diabetes: Second-line Therapy</u>

A recently published CADTH report provides recommendations for second-line therapy for patients with T2DM.[3] This report updates a 2013 version and includes evidence on new drugs and new drug classes that have become available since that time. A systematic review of oral and injectable antidiabetic agents was performed which identified 166 RCTs for inclusion in the review. Classes included were the following: SU, SGLT2 inhibitors, DPP-4 inhibitors, TZDs, GLP-1 RAs, alpha-glucosidase inhibitors, meglitinides and biphasic insulin.

The report provides two new recommendations.

1. **In patients with T2DM without established CV disease it is recommended that a SU be added to metformin for adults who are inadequately controlled on metformin alone.[3] Additional evidence is presented in Table 3.**
    a. A meta-analysis was preformed to support this recommendation which found A1C lowering of -0.58% to -0.94%.[3] There was no evidence of superiority of other classes to SU for safety or efficacy outcomes. Limitations to the review were a lack of evidence for long-term outcomes (e.g., CV events). Overall the evidence was defined as robust by the authors. Clinically significant hypoglycemia events were rare across all classes studied, including the incidence of severe hypoglycemia. SU were associated with a small increase in weight, approximately 2 kg.
    b. Evidence suggests that SU should be used with caution in elderly patients.

Table 3. Evidence Analysis for Recommendation 1[3]

Outcome	Evidence
Body Weight	When compared to metformin basal insulin and SU were associated with the most weight gain ranging from 2.1 kg to 2.8 kg. Statistically significant reductions in weight were found for GLP-1 RAs and SGLT2 inhibitors (-1.4 to -2.2 kg) when compared to metformin. Antidiabetic agents (non-insulin) added to metformin were associated with less weight gain compared to SU with a range of -1.9 to -4.3 kg. Compared to DPP-4 inhibitors both GLP1-RAs and SGLT2 inhibitors were found to reduce weight to a greater extent ($p < 0.05$).
Blood Pressure	When compared to metformin monotherapy all antidiabetic treatments lowered blood pressure diastolic blood pressure compared to baseline values except for SU ($p < 0.05$). The mean difference in diastolic blood pressure lowering was more for SGLT2 inhibitors combined with metformin compared to SU and DPP-4 inhibitors ($p < 0.05$).
Hypoglycemia	Severe hypoglycemia was more common with SU compared to metformin (OR 6.4%; 95% CI, 2.24 to 17.51). Comparisons between the classes demonstrated a reduced risk of severe hypoglycemia with GLP-1 RAs, SGLT2 inhibitors and DDP-4 inhibitors compared to SU. In metformin monotherapy comparisons, all antidiabetic treatments had a lower rate of nonsevere hypoglycemia compared to SU and basal and biphasic insulin. Biphasic insulin was associated with a higher rate of nonsevere hypoglycemia compared to basal insulin.
Mortality	Due to low event rates the meta-analysis for all-cause mortality and CV mortality were not robust. In an analysis of DPP-4 inhibitors compared to SU there was no difference in all-cause mortality (OR 1.19; 95% CI, 0.65 to 2.17) or CV mortality (OR 1.84; 95% CI, 0.66 to 5.12).
Adverse Events	In comparison to metformin no antidiabetic class was associated with a statistically significant increase or decrease in serious adverse events. Withdrawals were higher with SU, DPP-4 inhibitors, basal insulin, GLP-1 RAs when combined with metformin compared to metformin alone ($p < 0.05$). The total number of adverse events were higher with GLP-1 RAs, basal insulin and biphasic insulin compared to metformin.
Cholesterol	SGLT2 inhibitors increased low-density lipoprotein (LDL) cholesterol in comparison to metformin and DPP-4 inhibitors. Combinations of metformin and SGLT2 inhibitors were associated with an increase in high-density lipoprotein (HDL) cholesterol compared to metformin alone, SU, DPP-4 inhibitors, and GLP-1 RAs.
Heart Failure	Low events prevented strong conclusions on HF. Comparison of SU to DPP-4 inhibitors found no difference in HF rates (OR 1.35; 95% CI, 0.48 to 3.82).
Stroke and TIA	Low event rates prevented strong conclusions. No significant differences were found between metformin and SU, SGLT-2 and DPP-4 inhibitors.
Pancreatitis	Meta-analysis results were inconclusive due to low event rates.
Urogenital Adverse Events	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased urogenital adverse events.
Fractures	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased fracture rates (data not available for GLP-1 RAs).
Unstable Angina	No significant differences were found in comparisons of metformin to combinations of metformin and SU or SGLT2 inhibitors or DPP-4 inhibitors.

2. **In patients with T2DM and CV disease, therapy should be considered which has been has been specifically studied for this indication and recommendations have been previously provided by CADTH.[3] Additional evidence is presented in Table 4.**
    a. There is not enough evidence to support a recommendation for a specific drug class at this time based on 17 RCTs. All trials allowed patients to continue on varying regimens of background therapies.
    b. Previous reviews of the evidence recommend the use of empagliflozin for patients at high risk of CV events.

Table 4. Evidence Analysis for Recommendation 2 (Cardiovascular trials only)[3]

Outcome	Evidence
Major Adverse Cardiovascular Events	Evidence from 5 RCTs provided insufficient data to conclude that any antidiabetic class lowered the risk of MACE (composite endpoint of CV mortality, nonfatal MI, and nonfatal stroke).
Mortality	SGLT2 inhibitors reduced the risk of all-cause mortality when compared to placebo (OR 0.67; 95% CI, 0.47 to 0.95) or DPP-4 inhibitors (OR 0.66; 95% credible interval [CrI], 045 to 99). No other comparisons were available
Cardiovascular Mortality	None of the classes significantly lowered CV mortality when compared to placebo or to other antidiabetic classes.
Hospitalizations Due to Heart Failure	Data was insufficient to draw conclusions.
Adverse Events	None of the classes significantly increased or decreased the risk of adverse events, severe adverse events or withdrawals due to adverse events
Hypoglycemia	In comparisons of TZDs to existing therapies, TZDs were found to have the greatest risk of severe hypoglycemia (OR 2.05; 95% CI, 1.11 to 3.98); however, data was not available for SU or metformin.
Cancer	Compared to placebo TZDs significantly decreased pancreatic cancer based on 3 RCTS. In class comparisons TZDs also decreased the risk of pancreatic cancer when compared to GLP-1 RAs (OR 0.13; 95% CI, 0.01 to 0.75). Placebo and class comparisons found no increase in the risk of bladder cancer.
Pancreatitis	The risk of pancreatitis was not increased with DPP-4 inhibitors (OR 1.60; 95% CI, 0.97 to 2.66) or GLP-1 RAs (OR 0.73; 95% CI, 0.37 to 1.39) when compared to placebo or each other.
Fractures	No classes significantly increased or decreased fracture rates in comparison to each other or placebo based on 3 RCTs.

New Guidelines:

<u>The American Diabetes Association – Standards of Medical Care 2017</u>

The ADA updates their standards of care in diabetes each year.[5] The 2017 standards contain comprehensive recommendations for managing all aspects of patients with diabetes. ADA makes recommendations based on a systematic review or other review of the published literature and grading of the evidence. Recommendations are given a rating of A, B, C and E (**Table 5**). Statement of extensive literature search is included but specific methods are not described. Updates pertaining to the pharmacology of diabetes and treatment goals will be included in this review.

Table 5. ADA Evidence-grading System[5]

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
B	Supportive evidence from well-conducted cohort studies
C	Supportive evidence from poorly controlled or uncontrolled studies
E	Expert consensus or clinical experience

Recommendations:
Hemoglobin A1C goals – A goal of <7% is recommended for most patients based on level A evidence. A lower goal of <6.5% may be appropriate for those that are candidates for more intensive management without experiencing significant hypoglycemia (level C evidence). Patients with limited life expectancy, history of severe hypoglycemia and advanced complications may be more appropriately managed with a higher goal of <8% (level B evidence).[5]

Pharmacological Management of T2DM – Metformin is recommended first-line in patients without contraindications based on level A evidence.[5] Newly diagnosed patients presenting with an A1C of ≥10% or a blood glucose of ≥300 mg/dL should be considered candidates for insulin based on expert opinion (level E evidence). Dual therapy may be considered in patients presenting with A1C levels of ≥9%. If noninsulin monotherapy at maximal tolerated doses fails to control glucose levels to target ranges after 3 months, then an additional oral agent, basal insulin or a GLP-1 RA should be added (evidence level A). The most appropriate treatment to add to metformin is not clearly defined.[5] A meta-analysis found that newer classes of noninsulin therapies lowered A1C to a similar level of approximately 0.9-1.1%. If goal glycemic levels are not obtained with metformin monotherapy, a treatment from one of the following classes should be considered: SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 RA or basal insulin. If after 3 months the goal A1C is still not achieved, a third agent should be initiated. If triple therapy fails to get a patient to target A1C after an additional 3 months, then combination injectable treatment should be considered. The guidelines do not recommend one medication class over another after metformin. Treatments should be determined by patient-specific factors, such as risk for hypoglycemia, weight changes, adverse effects, and cost (evidence level E). Insulin therapy should not be delayed in patients who are not obtaining glycemic treatment goals (evidence level B). Empagliflozin or liraglutide should be considered for patients with a long history of diabetes who are not meeting glucose targets and have established atherosclerotic disease (evidence B) since both agents have shown to decrease cardiovascular and all-cause mortality when added to standard care in patients with preexisting cardiovascular disease.

<u>American College of Physicians – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus</u>
A 2017 update from the ACP evaluated oral treatment options for patients with T2DM and updated recommendations from 2012.[4] The recommendations were based on the AHRQ evidence review of oral agents for the treatment of T2DM (presented above). Evidence from randomized and observational studies were included. Study quality was assessed and evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Classes included in the review were TZDs, SUs, DPP-4 inhibitors and SGLT2 inhibitors and metformin.

Evidence was low or insufficient for clinical outcomes of mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy and neuropathy, based on data from 65 new studies.[4] Most antidiabetic therapies had similar efficacy in their ability to lower A1C.
ACP updated 2 recommendations:

1. Metformin should be prescribed to patients requiring glucose lowering therapy (strong recommendation; moderate-quality of evidence).[4]
2. If a second oral agent is required then either a SU, TZD, an SGLT2 inhibitor, or a DPP-4 inhibitor should be considered in addition to metformin (weak recommendation; moderate quality of evidence). Treatment selection should be made after a discussion of benefits, adverse effects and costs.[4]

NICE – Type 2 Diabetes in Adults

NICE updated several recommendations to its 2015 guidance on the management of T2DM.[8] Recommendations include a target A1C of 7.0% or less. If target A1C is not met with diet, lifestyle and adherence reinforcement, drug treatment should be considered. Metformin is recommended first-line in adults with T2DM. Metformin is not recommended in patients with an estimate glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2. Alternatives to metformin, if contraindicated or not tolerated, are: DDP-4 inhibitor, pioglitazone or SU. SGLT2 inhibitors are recommended instead of a DPP-4 inhibitors if SU or pioglitazone is not appropriate. Pioglitazone is not recommended in patients with HF, hepatic impairment, diabetic ketoacidosis, current or history of bladder cancer or uninvestigated macroscopic hematuria. In patients with symptoms of hyperglycemia, SU or insulin therapy should be considered.

Drug therapy intensification is also recommended in patients on monotherapy with an A1C above 7.5%.[8] Specific drug treatments should be based on efficacy, safety, comorbidities, polypharmacy, patient's preferences and needs and cost. Recommended combinations are: metformin and DPP-4 inhibitor, metformin and pioglitazone, metformin and a SU, or metformin and a SGLT2 inhibitor. In patients who are unable to take metformin, the following combinations are recommended: DPP-4 inhibitor and pioglitazone, DPP-4 inhibitor and a SU or pioglitazone and a SU.

The following triple therapies are recommended if needed: 1) metformin, DPP-4 inhibitor and SU 2) metformin, pioglitazone and SU 3) metformin, SGLT2 inhibitor, and pioglitazone or SU 4) insulin-based treatment.[8] If metformin and 2 other antidiabetic treatments fail to lower glucose levels to goal, are not tolerated or are contraindicated then metformin, a SU and GLP-1 RA should be considered in patients who have the following characteristics:1) a BMI of 35 kg/m2 or greater and psychological or other medical problems associated with obesity 2) a BMI of less than 35 kg/m^2 and who insulin therapy would have significant occupational implications 3) weight loss would benefit other significant obesity-related comorbidities. Use of GLP-1 RA should be monitored and only continued if there is at least a 1% reduction in A1C and at least a 3% weight loss within 6 months. In patients who are candidates for insulin, metformin therapy should be continued unless contraindicated or not tolerated. NPH insulin is recommended with or without short-acting insulin; however, this practice is less common in the United States (US). Insulin detemir or insulin glargine is recommended in patients who require assistance in insulin administration, experience lifestyle altering hypoglycemia, or the patient would require NPH and additional oral antidiabetic treatments.[8] Pre-mixed (biphasic) insulin analogues are recommended if injecting immediately before a meal, hypoglycemia is an issue or postprandial hyperglycemia is a concern. Patients who start on NPH insulin may need to be switched to insulin detemir or insulin glargine if target A1C levels are not reached due to hypoglycemia, or if the patient experiences significant hypoglycemia, has problems operating the NPH insulin device (not available in the US), or who require assistance in insulin administration.

Suggested intervals for monitoring A1C to assess goal attainment and response to therapy is every 3 months until A1C and treatment is stable, after that every 6 months is sufficient.

NICE – Recommendations for Dapagliflozin Triple Therapy in T2DM

In 2016 NICE updated guidance on the use of dapagliflozin in triple therapy regimens for adult patients with T2DM.[6] The guidance recommends dapagliflozin as one option as a triple therapy regimen in combination with metformin and a sulfonylurea (see below). Previous appraisals focus on the use of dapagliflozin as part of a dual therapy regimen. NICE recommends metformin first-line, followed by combination therapy if glucose targets are not obtained.

NICE – Canagliflozin, Dapagliflozin and Empagliflozin as Monotherapies for Treating Type 2 Diabetes

Based on an evidence review, NICE recently updated guidance for the use of 3 SGLT-2 inhibitors.[7] The guidance recommends canagliflozin, dapagliflozin or empagliflozin as an option in adult patients with T2DM that are unable to take metformin and diet and exercise fail to lower blood glucose levels to target after the following have been met:

- A DDP-4 inhibitor would otherwise be prescribed and
- A SU or pioglitazone is not appropriate

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm

An updated consensus statement was released by the AACE/ACE in 2017.[9] Recommendations are based on evaluating the evidence by giving the evidence a rating and evaluating the risk of bias. They also include a subjective factor impact and two-thirds expert consensus in the overall recommendation grade, which allows for high bias in recommendation development. Several authors have associations with industry that could influence recommendations. The strength of the recommendations were provided in a visual format based on a colored line but were not assigned an alphabetical recommendation grade which limits interpretation of the guidance.

Target A1C values of ≤ 6.5% are recommended if it can be reached safely and affordably. Pharmacotherapy recommendations are based on initial A1C level (**Table 6**).[9] Hemoglobin A1C should be reassessed every 3 months. Patients on monotherapy that are not meeting glucose targets after 3 months should be considered for dual therapy (**Table 6**). Patients who are not at goal using dual therapy are recommended to go to triple therapy (**Table 6**).

Table 6. AACE/ACE Glycemic Control Recommendations[9]

Entry A1C	Recommendations (in order of suggested hierarchy of usage)	
< 7.5%	1. Metformin 3. SGLT2 Inhibitors 5. TZD‡ 7. SU/GLN‡	2. GLP-1 RA 4. DPP-4 inhibitors 6. AGi
Dual Therapy: ≥ 7.5%* * In combination with metformin or other first-line agent	1. GLP-1 RA 3. DPP-4 inhibitors 5. Basal insulin‡ 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. TZD‡ 6. Colesevelam 8. AGi
Triple Therapy: ≥ 7.5%† † In combination with metformin or other first-line	1. GLP-1 RA 3. TZD‡ 5. DPP-4 inhibitor 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. Basal insulin‡ 6. Colesevelam 8. AGi 10. Add or intensify insulin therapy

agent + second-line agent	
< 9%	Symptoms: Insulin ± other agents No symptoms: Dual therapy or triple therapy
‡ These treatments are recommended to be used with caution due to adverse effects. Abbreviations: AGi = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase 4; GLP-1 RA = glucagon-like peptide receptor agonist; SGLT2 = sodium glucose cotransporter 2; TZD = thiazolidinedione	

Safety Alerts:

The FDA reviewed the risk of heart failure associated with the use of the DPP-4 inhibitors, saxagliptin and alogliptin, in February 2014.[12] In April 2016, they concluded that saxagliptin and alogliptin may increase the risk of heart failure, especially in patients with preexisting heart or kidney disease and. The FDA requested the manufacturers to update warning labeling for these drugs. The recommendation came from review of clinical trial data that demonstrated increased risk of hospitalizations in patients who received saxagliptin or alogliptin compared to placebo. The risk was 35 out of 1,000 patients for saxagliptin compared to 28 out of 1,000 for placebo. The risk was 39 out of 1,000 for alogliptin compared to 33 out of 1,000 for placebo. Therefore, the risk is approximately increased by 6-7 patients per 1000 with saxagliptin and alogliptin compared to placebo.

Pioglitazone may be associated with an increased risk of bladder cancer according to an updated review by the FDA in December of 2016.[10] The possible association of pioglitazone and bladder cancer was first identified in 2010 based on epidemiological data. Since then, additional studies have yielded conflicting results. One study found a trend towards higher risk with increased duration of use but results were not statistically significant (HR 1.06; 95% CI, 0.89 to 1.26). A second study found the risk of bladder cancer with pioglitazone, compared to placebo, was higher during the treatment period (RR 2.83; 95% CI, 1.02 to 7.85); however, during the 12.8 years of follow-up (trial and observational period) there was no increased risk identified (HR 1.0; 95% CI, 0.59 to 1.72). A retrospective cohort trial found the risk of bladder cancer with pioglitazone use was higher compared to no TZD use (HR of 1.63; 95% CI, 1.22 to 2.19). The FDA concluded that pioglitazone may increase the risk of bladder cancer and the label has been updated.

Labeling changes were required by the FDA for metformin-containing products in April of 2016.[13] The changes expanded the use of metformin for patients with diabetes with mild to moderate renal impairment when previously metformin was note recommended to be used in these patients. Recommendations were also added that eGFR be monitored annually. Metformin is still contraindicated in patients with an eGFR of less than 30 mL/min/1.73 m^2 and not recommended in patients with an eGFR of 30-45 mL/min/1.73 m^2.

A 2016 review found interim trial data that suggested canagliflozin may be associated with an increased risk of leg and foot amputations in patients with T2DM.[11] The suggested mechanism for this risk is unknown and the risk with other SGLT2 inhibitors has not been determined. Recent data released in May 2017 found that canagliflozin was associated with an increased risk of amputations based on analyses of two large clinical trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R). The incidence of amputations was 2-times higher in patients treated with canagliflozin compared to placebo. In the CANVAS study, the risk was 5.9 out of every 1,000 patients treated with canagliflozin compared to 2.8 out of every 1,000 patients treated with placebo. In the CANVAS-R study, the risk was 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 treated with placebo. Amputations were most common in the toe and middle of the foot. More extensive amputations involving the leg, below and above the knee have also occurred. Canagliflozin labeling has been updated with a black box warning to this effect.

New Formulations:

Insulin glargine/lixisenatide (Soliqua™ 100/33)

A combination formulation of the previously reviewed lixisenatide and insulin glargine was approved in 2016 as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM who are not controlled on basal insulin (less than 60 units daily) or lixisenatide.[14] The starting dose for patients that remain uncontrolled on 30 units or less of basal insulin or on lixisenatide is 15 units of the combination product (15 units of glargine/5 mcg lixisenatide) subcutaneously (SC) once daily. For patients using 30-60 units of basal insulin daily, who remain uncontrolled, the starting dose is 30 units (30 units of insulin glargine/10 mcg lixisenatide) given SC once daily. The maximum daily dose is 60 units (60 units of insulin glargine/20 mcg lixisenatide) SC daily. Injection should be administered one hour prior to the first meal of the day.

Insulin glargine/lixisenatide was approved based on one open-label, 30-week, active-controlled, multicenter, RCT in patients with T2DM.[14] Insulin glargine/lixisenatide 100/33 was compared to insulin glargine 100 units/mL in 736 patients. Patients with a 12-year history of diabetes were followed for 30 weeks after a 6-week run-in and stabilization phase. Insulin glargine/lixisenatide treated patients had lower A1C levels compared to insulin glargine alone (6.9% vs. 7.5%, respectively; MD -0.5%; 95% CI, -0.6 to -0.4%: p<0.01). The dose of insulin glargine was capped at 60 units to determine the efficacy of the GLP-1 RA component. The doses of insulin glargine at the end of the trial were similar between groups.

Dapagliflozin/saxagliptin (Qtern®)

The combination product of the SGLT-2 inhibitor, dapagliflozin, and the DPP-4 inhibitor, saxagliptin, was approved for the treatment of patients with T2DM as an adjunct to diet and exercise who have inadequate glycemic control with dapagliflozin or are already being treated with dapagliflozin and saxagliptin.[15] The combination tablet of dapagliflozin 10 mg and saxagliptin 5 mg should be taken once daily in the morning.

The dapagliflozin/saxagliptin combination was approved based on one 24-week, double-blind, placebo-controlled trial in 315 patients with T2DM. Patients who were on dapagliflozin and metformin and remained uncontrolled were randomized to saxagliptin or placebo.[15] At week 24, patients receiving dapagliflozin, metformin and saxagliptin had greater A1c lowering compared to patients taking dapagliflozin, metformin and placebo (MD -0.4%; 95% CI, -0.4 to -0.2; p<0.0001).

Insulin degludec/liraglutide (Xultophy® 100/3.6)

A combination formulation insulin degludec, a long-acting insulin, and liraglutide, a GLP-1 RA, was approved in 2016.[16] The combination product is approved as an adjunct to diet and exercise in patients with T2DM who have hyperglycemia despite basal insulin (less than 50 units a day) or liraglutide (less than or equal to 1.8 mg daily). The recommended starting dose is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given SC once daily with a maximal dose of 50 units (50 units insulin degludec and 1.8 mg liraglutide).

Three RCTs were used for the approval of insulin degludec/liraglutide. All trials had a duration of 26 weeks in a total of 1393 patients with T2DM.[16] In an open-label comparison between insulin degludec/liraglutide versus liraglutide 1.8 mg in patients on stable oral antidiabetic treatments, insulin degludec/liraglutide resulted in an A1C reduction of -1.31% compared to -0.36% in the liraglutide group (MD -0.95%, 95% CI, -1.15 to -0.75%; p<0.001). A second double-blind trial evaluated insulin degludec/liraglutide compared to insulin degludec once daily in patients taking metformin. Insulin degludec/liraglutide decreased A1C by 1.95% compared to a decrease of 1.05% for insulin degludec at week 26 (MD -0.89% (95% CI, -1.10 to -0.68%). Insulin degludec doses were kept to a similar level to determine contribution of liraglutide to the combination; therefore, the clinical effect of insulin degludec may have been diminished by titration restrictions.

The last trial was an open-label comparison of insulin degludec/liraglutide versus insulin glargine in patients with T2DM who were on metformin. At 26 weeks, A1C decreased by 1.67% in patients taking insulin degludec/liraglutide compared to 1.16% in patients taking insulin glargine. Insulin degludec/liraglutide was found to be non-inferior to insulin glargine (MD -0.51%, 95% CI, -0.67 to -0.34; p<0.01).[16]

Canagliflozin/metformin ER (Invokamet XR)

A new combination product of canagliflozin and metformin ER was approved in 2016 for the treatment of patients with T2DM as an adjunct to diet and exercise in adults with T2DM.[17] Canagliflozin/metformin ER is available 4 different strengths: canagliflozin 50 mg with metformin ER 500 mg or 1000 mg and canagliflozin 150 mg with metformin ER 500 mg or 1000 mg. Maximum recommended dose is canagliflozin 300 mg daily/metformin ER 2000 mg daily. Approval of canagliflozin/metformin ER was based on previous study data that compared canagliflozin and metformin to other active treatments.

Randomized Controlled Trials:

One thousand fifty-two potentially relevant clinical trials were evaluated from the literature search. After further review, only 4 trials were included (**Table 7**). Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trials are briefly described in the table below. The full abstracts are included in Appendix 2.

Table 7. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Outcomes	ARR/NNT	Quality Rating
1. Marso, et al (LEADER)[18] RCT, DB, MC, Phase 3	1. Liraglutide 1.8 mg SC (L)* ‡ 2. Placebo SC (P)* * In addition to standard care ‡ or the maximum tolerated dose 3.5 years	Demographics: Age: 64 years Male: 64% A1C: 8.7% DM duration: 13 yrs. Established CV disease: 81.3% CKD: 72.4% Any antidiabetic mediations: 88% Metformin use: 76% SU use: 50% Key Inclusion Criteria: - T2DM - A1C ≥ 7%	ITT: 1.4668 2.4672 PP: 1. 4529 2. 4513 Attrition: 1. 139 (3.0%) 2. 159 (3.4%)	**Composite of CV death, non-fatal MI, and non-fatal stroke at 36 months:** L: 608 (13.0%) P: 694 (14.9%) HR 0.87 (95% CI, 0.78 to 0.97; P<0.001 for noninferiority and P=0.01 for superiority) **Death from CV causes:** L: 219 (4.7%) vs. P: 278 (6.0%) HR 0.78 (95% CI, 0.66 to 0.93; P=0.007) **Death from any cause:** L: 381 (8.2%) vs. P: 447 (9.6%)	ARR 1.9/53 ARR 1.3/77	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: (low) Patients were randomized in a 1:1 ratio by interactive voice/web response system. Performance: (unclear) Trial was double-blind design but no details on blinding were provided. Detection: (low) Outcome assessment was adjudicated in a blinded fashion by an external, independent, event-adjudication committee. Attrition: (low) Overall attrition was low and similar between groups. ITT analysis was used for all data. Discontinuations without an outcome were censored from the day of last visit and any future outcomes were not included. Publication: (high) The study was funded by Novo Nordisk, the manufacturer of liraglutide, and the National Institutes of Health. **Applicability**: Patients: Patients were well matched at baseline for most characteristics. There were more patients in the placebo group that received SU, TZDs

		- Currently on DM therapy or naïve to treatment - ≥ 50 yo + ≥1 CV coexisting condition or ≥ 60 years + ≥1 CV risk factor <u>Key Exclusion Criteria</u>: - T1DM - Use of GLP-1 RA, DPP-4 inhibitor, pramlintide, or rapid-acting insulin - MEC or medullary thyroid cancer - Acute coronary event or CV event within 14 days of screening and randomization		HR 0.85 (95% CI, 0.74 to 0.97; P=0.02) <u>**Secondary Outcomes**</u> **Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or heart failure:** L: 948 (20.3%) vs. P: 1062 (22.7%) HR 0.88 (0.81 to 0.96; P=0.005) **Renal and retinal microvascular outcome:** L: 355 (7.6%) vs. P: 416 (8.9%) HR 0.84 (95% CI, 0.73 to 0.97; P= 0.02)	ARR 1.4/71 ARR 2.4/42 ARR 1.3/77	and insulin which may negatively influence cardiac effects which may bias results in favor of liraglutide. Patients were most likely older than the majority of patients with Medicaid. <u>Intervention</u>: FDA approved dose of liraglutide. Median daily study dose was 1.78 mg. <u>Comparator</u>: Matched placebo. <u>Outcomes</u>: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated with unacceptable levels of cardiac risk. <u>Setting</u>: Thirty-two countries and 410 centers. Thirty percent of patients were enrolled in North American treatment centers. **Analysis**: In patients with T2DM liraglutide was more effective at reducing the risk of death and death from CV causes in patients on standard therapy and had a history of CV disease. Subgroup analysis found that patients with an eGFR of < 60 ml/min/1.73 m^2 may be most likely to benefit from liraglutide.
2. Gadde, et al (DURATION-NEO-2)[19] RCT, OL, MC, Phase 3	1. Exenatide QWS-AI 2 mg SC (E) 2. sitagliptin 100 mg PO daily (S) 3. Placebo SC (P) 28 weeks	<u>Demographics</u>: Age: 53 years Male: 55% A1C: 8.5% DM duration: 8.4 yrs. White: 81% Body mass index: 31.7 kg/m2 <u>Key Inclusion Criteria</u>: - T2DM - A1C ≥ 7.1 -11.0% - FPG < 280 mg/dL - Currently on metformin ≥ 1500 mg for at least 2 months - BMI ≤ 45 kg/m2 <u>Key Exclusion Criteria</u>:	<u>mITT</u> E: 181 S: 122 P: 61 Attrition: E: 26 (14%) S: 13 (11%) P: 14 (23%)	**Change in A1C at 28 weeks:** E: -1.13% S: -0.75% P: -0.40% E vs. S: LSM -0.38 (95% CI, -0.70 to -0.06) P = 0.021 E vs. P: LSM -0.72 (95% CI, -1.15 to -0.30) P = 0.001 <u>**Secondary Outcomes**</u> **A1C < 7%:** E: 43.1% S: 32% P: 24.6%	NA NA E vs. S: ARR 11.1/9	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized in a 3:2:1 ratio by interactive web response system and stratified by A1C level. <u>Performance</u>: (high) Trial was open-label design. All staff, providers and patients were blinded to placebo or sitagliptin randomization. <u>Detection</u>: (low) Outcome assessment performed in a blinded manner. <u>Attrition</u>: (high) Attrition varied between groups and was substantial in the placebo group. <u>Publication:</u> study funded by the manufacturer. **Applicability**: <u>Patients</u>: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. <u>Intervention</u>: FDA approved dose of exenatide weekly. <u>Comparator</u>: Sitagliptin 100 mg and placebo comparison appropriate. <u>Outcomes</u>: A1C is an accepted surrogate end point used for evaluating the efficacy of glucose lower therapy. Health outcomes, such as mortality, macrovascular and microvascular effects would be more helpful. <u>Setting</u>: Eighty-one treatment centers in the US.

		- eGFR < 30 mL/min/1.73 m^2 - Use of GLP-1 RA, DPP-4 inhibitor, SU, TZD or weight loss medications within 3 months of screening - ≥ 2 episodes of severe hypoglycemia within previous 6 months		P < 0.05 for both comparisons (no CI provided) **Body weight:** E: -1.12 kg S: -1.19 kg P: 0.15 kg E vs. S: LSM 0.1 kg (95% CI, -0.70 to 0.9) P = 0.863 E vs. P: LSM -1.3 (95% CI, -2.3 to -0.2) P = 0.20	E vs. P: ARR 18.5/5 NS NS	**Analysis**: In patients with T2DM exenatide used once weekly was more effective than sitagliptin and placebo w/ similar effect on weight. A majority of patients experienced anti-exenatide antibodies which reduced effect on A1C in patients w/ high levels.
3. Kernan, et al (IRIS)[20] RCT, DB, MC, Phase 3	1. Pioglitazone 45 mg daily (PZ) 2. Placebo (P) 4.8 years	Demographics: Age: 63 years Male: 66% Fasting glucose: 98 mg/dL (pre-diabetic) Stroke: 87% HTN: 71% Key Inclusion Criteria: - ≥ 40 years - Ischemic stroke or TIA - HOMA IR ≥3.0 Key Exclusion Criteria: - Diabetes diagnosis - NYHA Class III or IV - Liver disease - Pitting edema	ITT PZ: 1939 P: 1937 Attrition: PZ: 175 (9%) P: 151 (8%)	**Fatal or non-fatal stroke or MI:** PZ: 175 (9.0%) P: 228 (11.8%) HR 0.76; 95% CI, 0.62 to 0.93 P = 0.007 **Secondary Outcomes** **All-cause mortality:** PZ: 136 (7%) P: 146 (7.5%) HR 0.93; 95% CI, 0.73 to 1.17 P = 0.53 **Fractures:** PZ: 99 (5.1%) P: 62 (3.2%)	 ARR 2.8/36 NS ARR 1.9/53	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: (low) Patients were randomized in a 1:1 ratio by random permuted block design. Performance: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. Detection: (unclear) Endpoints will be assessed and adjudicated by three separate review committees for stroke, MI/CV and diabetes. Blinding was not described. Attrition: (low) Attrition was low in both groups. ITT was used for data analysis. Publication: (high) Authors had ties to industry. Funding provided by a grant from the National Institute of Neurological Disorders and Stroke. **Applicability**: Patients: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. Intervention: FDA approved dose of pioglitazone. Comparator: Placebo comparison appropriate in this population. Outcomes: Stroke is an important health outcome.

		- Risk of bladder cancer		P = 0.003 **Diabetes Developed:** PZ: 73 (3.8%) P: 149 (7.7%) HR 0.48; 95% CI 0.33 to 0.69 P < 0.001	ARR 3.9/26	Setting: Sixty-seven percent were from treatment centers in the US. **Analysis**: The results of this study shows a reduced risk of stroke in patients with pre-diabetes and history of stroke or TIA. The incidence of patients developing diabetes was low so applicability to patients with a diabetes diagnosis is low; however, due to lack of data in this area, the findings are still of clinical value.
3. Neal, et al (CANVAS Program)[21] RCT, DB, MC, Phase 3	1. Canagliflozin 100 mg and 300 mg daily*ł (C) 3. Placebo* (P) * Background antidiabetic therapy was permitted ł Results are a combination of two trials 188 weeks follow-up	Demographics: Age: 63 years Male: 64% Diabetes history: 13.5 years CV disease: 65.6% White: 78% Baseline A1C: 8.2% Key Inclusion Criteria: - A1C ≥ 7% or ≤ 10.5% - ≥ 30 years with symptomatic atherosclerotic CV disease OR ≥ 50 years with 2 or more CV risk factors - eGFR of > 30 ml/min/1.73 m^2 Key Exclusion Criteria: - Diabetes diagnosis - NYHA Class III or IV - Liver disease - Pitting edema - Risk of bladder cancer	ITT C: 5795 P: 4347 Attrition: C: 224 (3.9%) P: 184 (4.2%)	**Composite of CV death, non-fatal MI, and non-fatal stroke:** C: 585 (10.1%) P: 426 (11.4%) HR 0.86; 95% CI, 0.75 to 0.97 P < 0.001 **Secondary Outcomes** **All-cause mortality:** C: 400 (13.8%) P: 281 (15.7%) HR 0.87 (95% CI, 0.72 to 1.06) P = 0.24 **Death from CV causes:** C: 268 (9.3%) P: 185 (10.4%) HR 87 (95% CI, 0.72 to 1.06) P = NS **Progression to albuminuria:** C: 1341 (51.3%) P: 1114 (62.0%) (HR 0.73; 95% CI, 0.67 to 0.79)	ARR 1.3%/77 NS NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: (low) Patients were randomized thru an interactive web-based response system with the use of a computer-generated randomization schedule. Performance: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. Detection: (unclear) Endpoints will be assessed and adjudicated by three separate review committees for stroke, MI/CV and diabetes. Blinding was not described. Attrition: (low) Attrition was low in both groups. ITT was used for data analysis. Publication: (high) Industry funded study. **Applicability**: Patients: A majority (71.4%) of patients took canagliflozin 300 mg and had CV disease or where at high risk for developing CV disease. Fifty percent of patients were on other antidiabetic treatments at baseline and 75% were on cardioprotective treatments. Intervention: FDA approved dose of canagliflozin. Comparator: Placebo comparison appropriate in this population. Outcomes: CV outcomes are more common in this population compared to patients without diabetes therefore, the CV impact of antidiabetic treatments are of particular importance. Setting: Thirty countries and 667 centers. Safety Warning: A higher number of patients who received canagliflozin had amputations compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75) (ARR not provided). **Analysis**: In patients with CV disease or who are high risk of CV disease, canagliflozin reduced the composite of CV endpoints but not any individual endpoints when compared to placebo. Patients at high risk of CV disease who are also on cardioprotective medications (e.g., ACE inhibitors) may receive cardiovascular benefit from canagliflozin but also have a higher risk of amputations.

Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; CKD = chronic kidney disease; CV = cardiovascular; DB = double-blind; DD = double-dummy; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; FAS = full analysis set; FPG = fasting plasma glucose; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance index; HR = hazard ratio; HTN = hypertension; ITT = intention to treat; kg = kilogram; LSMD = least-squares mean difference; MEC = multiple endocrine neoplasia; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; NYHA = New York Heart Association; PO = by mouth; PP = per protocol; QWS-AI = once-weekly suspension for autoinjection; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; yo = years old.

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Appendix 1: Current Status on Preferred Drug List

Diabetes, Dipeptidyl Peptidase-4 Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**JANUMET**	**SITAGLIPTIN PHOS/METFORMIN HCL**	**Y**
ORAL	**TABLET**	**JANUVIA**	**SITAGLIPTIN PHOSPHATE**	**Y**
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN /METFORMIN HCL	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN MONOHYDRATE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N

Diabetes, GLP-1 Receptor Agonists & Amylin Analogs

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN INJCTR	SYMLINPEN 120	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	SYMLINPEN 60	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	BYETTA	EXENATIDE	N
SUB-Q	PEN INJCTR	VICTOZA 2-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	XULTROPHY	INSULIN DEGLUDEC/LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-Q	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-Q	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-Q	PEN INJCTR	TRULICITY	DULAGLUTIDE	N
SUB-Q	PEN INJCTR	ADLYXIN	LIXISENATIDE	N
SUB-Q	PEN INJCTR	SOLIQUA	INSULIN GLARGINE/LIXISENATIDE	N

Diabetes, Oral Hypoglycemic

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**DIABETA**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLYBURIDE**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLIPIZIDE**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**GLUCOTROL**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**AMARYL**	**GLIMEPIRIDE**	**Y**
ORAL	**TABLET**	**GLIMEPIRIDE**	**GLIMEPIRIDE**	**Y**
ORAL	**TAB ER 24H**	**GLUCOPHAGE XR**	**METFORMIN HCL**	**Y**
ORAL	**TAB ER 24H**	**METFORMIN HCL ER**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**GLUCOPHAGE**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**METFORMIN HCL**	**METFORMIN HCL**	**Y**
ORAL	TABLET	TOLBUTAMIDE	TOLBUTAMIDE	N
ORAL	TABLET	CHLORPROPAMIDE	CHLORPROPAMIDE	N
ORAL	TABLET	TOLAZAMIDE	TOLAZAMIDE	N
ORAL	TAB ER 24	GLIPIZIDE ER	GLIPIZIDE	N
ORAL	TAB ER 24	GLIPIZIDE XL	GLIPIZIDE	N
ORAL	TAB ER 24	GLUCOTROL XL	GLIPIZIDE	N
ORAL	TABLET	GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	GLYNASE	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	PRANDIN	REPAGLINIDE	N
ORAL	TABLET	REPAGLINIDE	REPAGLINIDE	N
ORAL	TABLET	NATEGLINIDE	NATEGLINIDE	N
ORAL	TABLET	STARLIX	NATEGLINIDE	N
ORAL	SOLUTION	RIOMET	METFORMIN HCL	N
ORAL	TAB ER 24	FORTAMET	METFORMIN HCL	N
ORAL	TAB ER 24	METFORMIN HCL ER	METFORMIN HCL	N
ORAL	TABERGR24H	GLUMETZA	METFORMIN HCL	N
ORAL	TABLET	ACARBOSE	ACARBOSE	N
ORAL	TABLET	PRECOSE	ACARBOSE	N
ORAL	TABLET	GLYSET	MIGLITOL	N
ORAL	TABLET	GLUCOVANCE	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLYBURIDE-METFORMIN	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	N
ORAL	TABLET	PRANDIMET	REPAGLINIDE/METFORMIN HCL	N

Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	QTERN	DAPAGLIFLOZIN/SAXAGLIPTIN	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY	EMPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN HCL	N

Diabetes, Thiazolidinediones

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**PIOGLITAZONE HCL**	**PIOGLITAZONE HCL**	**Y**
ORAL	TABLET	AVANDIA	ROSIGLITAZONE MALEATE	N
ORAL	TABLET	AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	N
ORAL	TABLET	DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	N
ORAL	TABLET	PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	N
ORAL	TBMP 24HR	ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	N

Appendix 2: Abstracts of Clinical Trials

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators.

BACKGROUND:

The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS:

In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS:

A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS:

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.).

Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study.

Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P; DURATION-NEO-2 study investigators.

AIMS:

Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors treat type 2 diabetes through incretin-signaling pathways. This study compared the efficacy and safety of the glucagon-like peptide-1 receptor agonist exenatide once-weekly (Miglyol) suspension for autoinjection (QWS-AI) with the dipeptidyl peptidase-4 inhibitor sitagliptin or placebo.

MATERIALS AND METHODS:

In this open-label, multicentre study of patients with type 2 diabetes who had suboptimal glycaemic control on metformin monotherapy, 365 patients were randomized to receive exenatide 2.0 mg QWS-AI, sitagliptin 100 mg once daily or oral placebo (3:2:1 ratio). The primary endpoint was change in glycated hemoglobin (HbA1c) from baseline to 28 weeks.

RESULTS:
At 28 weeks, exenatide QWS-AI significantly reduced HbA1c from baseline compared to sitagliptin (-1.13% vs -0.75% [baseline values, 8.42% and 8.50%, respectively]; P = .02) and placebo (-0.40% [baseline value, 8.50%]; P = .001). More exenatide QWS-AI-treated patients achieved HbA1c <7.0% than did sitagliptin- or placebo-treated patients (43.1% vs 32.0% and 24.6%; both P < .05). Exenatide QWS-AI and sitagliptin reduced fasting plasma glucose from baseline to 28 weeks (-21.3 and -11.3 mg/dL) vs placebo (+9.6 mg/dL), with no significant difference between the 2 active treatments. Body weight decreased with both active treatments (-1.12 and -1.19 kg), but not with placebo (+0.15 kg). No improvement in blood pressure was observed in any group. The most common adverse events with exenatide QWS-AI were gastrointestinal events and injection-site reactions.
CONCLUSIONS:
This study demonstrated that exenatide QWS-AI reduced HbA1c more than sitagliptin or placebo and was well tolerated.

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack.
Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR; IRIS Trial Investigators.
Abstract
BACKGROUND:
Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.
METHODS:
In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.
RESULTS:
By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).
CONCLUSIONS:
In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2017
Search Strategy:

#	Searches	Results
1	Sitagliptin Phosphate/	970
2	alogliptin.mp.	264
3	saxagliptin.mp.	380
4	linagliptin.mp. or Linagliptin/	342
5	pramlintide.mp.	303
6	exenatide.mp.	2168
7	liraglutide.mp. or Liraglutide/	1214
8	albiglutide.mp.	68
9	dulaglutide.mp.	79
10	glyburide.mp. or Glyburide/	4041
11	glipizide.mp. or Glipizide/	602
12	glimepiride.mp.	964
13	Metformin/ or metformin.mp.	12206
14	tolbutamide.mp. or Tolbutamide/	1662
15	chlorpropamide.mp. or Chlorpropamide/	218
16	tolazamide.mp. or Tolazamide/	22
17	repaglinide.mp.	633
18	nateglinide.mp.	473
19	acarbose.mp. or Acarbose/	1595
20	miglitol.mp.	195
21	dapagliflozin.mp.	285
22	canagliflozin.mp. or Canagliflozin/	286
23	empagliflozin.mp.	277
24	pioglitazone.mp.	4165
25	rosiglitazone.mp.	5289
26	lixisenatide.mp.	133
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	31226

28	limit 27 to (english language and humans and yr="2015 -Current")	3214
29	limit 28 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	1052

Appendix 4: Prior Authorization Criteria

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All DPP-4 inhibitors

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #4	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class	No: Approve for up to 12 months

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *7/17 (KS), 9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *1/15; 9/14; 1/14; 2/13*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All GLP-1 receptor agonists

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness.
3. 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 and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class	No: Go to #4
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
5. Is the patient currently taking insulin?	Yes: Go to #6	No: Approve for up to 12 months
6. Is the patient requesting exenatide, liraglutide, ~~or~~ albiglutide, dulaglutide or lixisenatide (including combination products) and using basal insulin?	Yes: Approve for up to 12 months	No: Go to #7
7. Is the patient requesting dulaglutide and using prandial insulin?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *2/15; 1/14*

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All SGLT-2 inhibitors

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	Yes: Go the Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #6

Approval Criteria		
6. Has the patient tried and failed all of the following drugs, or have contraindications to these drugs? • Insulin • Thiazolidinedione • DPP-4 inhibitor • GLP-1 agonist • Amylin analog	Yes: Approve for up to 6 months.	No: Pass to RPh; deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for up to 6 months.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13*
Implementation: *2/15*

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

New Drug Evaluation: Nusinersen Injection, Intrathecal

Date of Review: July, 2017
Generic Name: Nusinersen
PDL Class: Miscellaneous

End Date of Literature Search: 06/01/17
Brand Name (Manufacturer): Spinraza™ (Biogen)
AMCP Dossier Received: Yes

Research Questions:

1. What is the efficacy and effectiveness of nusinersen in reducing symptoms, improving functional outcomes and improving mortality in patients with spinal muscular atrophy (SMA)?
2. What are the harms of nusinersen in SMA patients?

Conclusions:

- The efficacy of nusinersen in improving motor function in infants with SMA type 1 was evaluated in one unpublished, low quality phase 3 trial with a high risk of bias.[1] At 6 months into the 13 month trial design the study was halted and became a nonrandomized observational study without intent to treat analysis. Primary and secondary outcomes were revised; the definition of the new primary outcome was changed, and the 78 (65%) of 122 original subjects who had not died, become ventilator dependent or withdrawn from the study became the new analysis group. Response was defined as a participant who was alive and participating in the study and demonstrated at least a two-point (level) increase in the ability to kick or a one-point increase using the HINE-2 assessment in head control, rolling, sitting, crawling, standing, or walking. A greater percentage of subjects achieved a one point change in Hammersmith Infant Neurological Exam (HINE) motor milestone response from baseline to the 6 month assessment in the nusinersen group (40%) compared to the control group (0%)($p<0.0001$).[2] There is insufficient evidence to evaluate long-term effects on survival, clinical course and ventilator dependency at this time.
- There is insufficient data to evaluate nusinersen safety at this time due to small sample sizes and short term trials.
- Nusinersen may increase the risk of bleeding complications due to thrombocytopenia; thrombocytopenia developed in 6 of 56 (11%) patients after administration of nusinersen in the Phase 3 clinical trial. None of the patients in the control cohort developed thrombocytopenia. Platelet testing is required at baseline and before each dose.[2]
- Nusinersen also has a risk for renal toxicity. Proteinuria occurred in 17 of 51 (33%) nusinersen patients compared to 5/25 (20%) sham control subjects during the Phase 3 clinical trial. Quantitative spot urine testing for proteinuria is required at baseline and prior to each dose.[2]
- Additional trials in patients with SMA types 2 and 3 are currently ongoing and not published. At this time, there is insufficient evidence of the safety and efficacy in these SMA populations.

Recommendations:

- Revise PA criteria to insure nusinersen utilization in SMA populations in which the drug is been studied.

- Consider referring nusinersen to the Health Evidence Review Commission (HERC) for funding placement as a medication with high cost and marginal clinical benefit.

Background:
SMA is characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles, and hypotonia. SMA is caused by homozygous deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13.[3] The SMN gene region consists of two almost identical genes: SMN1 and SMN2.[4] The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced truncated and nonfunctional SMN protein.[4] Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), a small part (10–15%) of the mRNA transcripts contains exon 7, resulting in a normal SMN protein.[4] The number of copies of SMN2 correlate with the functional status of SMA.[4] The majority of the severely affected patients with SMA type 1 have two SMN2 copies with a level of functional SMN protein of approximately 20 to 30%.[5] The presence of 3 or more copies of SMN2 is associated with milder SMA symptoms.

SMA is a rare disease, and the incidence ranges from 1 to 10 per 100,000 live births.[4] However, SMA is the most common genetic cause of death in infants.[4] The phenotype is extremely variable, and patients are classified as SMA type 0-IV based on age at onset and clinical course. SMA type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[3] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. These infants rarely achieve improvements in motor function or acquire motor developmental milestones.[4] Children with SMA type 2 exhibit muscle weakness that is more prominent in the lower extremities. They are able to sit unassisted, but are never able to independently walk. Respiratory failure is less severe and develops later in life compared to children with SMA type 1.[4] Children with SMA type 3 develop variable muscle weakness after 18 months of age and are able to walk. However, as the disease progresses, they may become wheelchair bound. Respiratory muscles are rarely affected and life expectancy is normal in this group of SMA patients.[4] SMA type 4 generally occurs in the second or third decade of life and is the mildest form of the disease characterized by mild muscle weakness and normal life expectancy. The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[4]

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1%
I	2	1 - 6 months	Never able to sit unassisted	<2 years	3.2 – 7.1 (45% of cases)
II	2-4	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
III	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5 – 4.6 (30 % of cases)
IV	4-8	10 - 30 years	Ambulatory	Normal	5% of cases

*Natural history may vary depending on supportive interventions

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60.[6] It is not possible to predict the severity of the SMA phenotype from carrier screening. Several methods for newborn

screening have been developed to diagnose SMA from DNA extracted from newborn blood spots. Methods include a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis to identify SMN1 and SMN2 deletions and quantify copy numbers of both genes, and real-time polymerase chain reaction.[5]

Due to the difficulties in quantifying motor abilities in these patients, several functional motor scales were developed to assess functional status in children with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients.[7] The assessment incorporates the limited abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16 item assessment of functional muscle strength and is scored on a 0–4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a maximum score of 64 points. It was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months). The relationship between CHOP INTEND scores correlated with subject age ($r = -0.51$, $p = 0.007$) and BiPAP utilization ($r = -0.74$, $P < .0001$).[8] The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[9] It includes 26 items assessing cranial nerve function, posture, quality and quantity of movements, muscle tone, and reflexes and reactions. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0 to 78). At 9 or 12 months, a score greater than or equal to 73 is considered optimal.[9] Sequential use of the HINE allows for the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[10] For example, in preterm infants assessed between 6 and 15 months corrected age, scores greater than 64 predict independent walking with a sensitivity of 98% and specificity of 85%.[10] Conversely, scores less than 52 are highly predictive of cerebral palsy and other severe motor impairments.[10] The HINE-2 screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[5] Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 78.[11] The Hammersmith Functional Motor Scale (HFMS) was developed by physical therapists to assess SMA type 2 and 3 patients.[12] The assessment provides information on motor ability and clinical progression in children with limited amubulation.[12] The HFMS motor assessment includes upper and lower limb activities as well as head and trunk control. Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4 point kneeling, crawling and standing. Each item is scored on a 3 point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter-observer agreement greater than 99%.[12] For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running, and jumping which resulted in the HFMSE (HFMS Extended) score.[13] It is scored on a 3 point scale similar to the HFSME, but scores range from 0 to 66. The Upper Limb Module (ULM) is used in non-ambulatory patients greater than 2 years of age.[14] This assessment was designed to assist in evaluating the ability of young children to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. The Six-Minute Walk Test is used only in ambulatory SMA patients more than 4 years of age.[15] The different motor function tests used in nusinersen trials are summarized in **Table 1**.

Table 1. Motor Function Assessments used in SMA trials

Test	Description	Score	SMA Patient Population
CHOP INTEND	Measure motor function in 16 items to assess neck, trunk, and limb strength	0 (least function to 4 (most function) Maximum score = 64 points	Presymptomatic and Infantile Onset
HINE-2	Measure functional ability and motor milestones in 26 items	0 (least function) to 4 (most function) Maximum score = 78 points	Presymptomatic and Infantile Onset
HFSM	Head, trunk, upper, and lower limb control on 20 items	0 = inability 1 = needs assistance 2 = unaided Maximum score = 40 points	Presymptomatic and Infantile Onset
HFSME	Added 13 additional items to HFSM to assess walking, running and jumping for a total of 33 items	0 = inability 1 = needs assistance 2 = unaided Maximum score = 66 points	Later Onset (types 2 and 3) – Ambulatory Patients

Abbreviations: CHOPINTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSM = Hammersmith Functional Motor Scale; HFSME = Hammersmith Functional Motor Scale Expanded; HINE =Hammersmith Infant Neurological Exam

There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Difficulties in feeding and swallowing can lead to lower respiratory infection, gastrointestinal complications and malnutrition. Full time noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Nusinersen is the first Food and Drug Administration (FDA) approved therapy for treatment of SMA. It is an antisense oligonucleotide which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein. As a result, the amount of functional SMN protein increases which can partially compensate for mutations/deletions of the SMN1 gene. Nusinersen must be administered intrathecally. Treatment is initiated with 4 loading doses; the first three doses are administered every 2 weeks, and the fourth dose is given 30 days after the third dose. Maintenance doses are given every 4 months.

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

Clinical Efficacy:

The U.S. Food and Drug Administration (FDA) approved nusinersen based on an interim analysis of a phase 3, multicenter, randomized, double blind, sham controlled study of nusinersen in 121 patients with infantile-onset SMA (ENDEAR). The trial has not been published as of June 2017. Details of this study were accessed from the summary report of nusinersen posted on the FDA website and the clinical trials.gov website.[1,16] Due to the orphan drug status of nusinersen, the FDA approval was fast tracked. Participants included in the trial were diagnosed with SMA symptoms before 7 months of age, were born between 37 and 42 weeks, and had 2 copies of the SMN gene. The nusinersen dose was 12 mg (or a scaled equivalent dose based on body weight) intrathecally on days 1, 15, 29, and 64 (loading dose) followed by 12 mg maintenance dosing every 4 months for 2 additional doses (days 183 and 302). The duration of the trial was 10 months. Interim analysis was based on the 78 (65%) of the original 121 subjects who had not died, become ventilator dependent, or withdrawn from the study at 6 months into the 13 month study design. The FDA approved a request to exchange the primary and secondary outcomes, redefine the new primary outcome, to

not perform statistical analysis on any outcomes except the new primary outcome, and to not perform intent-to-treat analysis. This had the effect of losing the benefits of randomization. Differences between the sample of 78 subjects and the original 121 subjects were not analyzed, so selection bias could not be assessed. Interim analysis was performed by an unblinded contract research organization and reviewed by the unblinded senior management team from Ionis and Biogen. The management team was prohibited by the FDA to have further involvement in the study. The original primary outcome was time to death or permanent ventilation during the 13 month follow-up period. Prior to the interim analysis, the investigators added an additional efficacy endpoint to include assessment of the proportion of responders achieving motor milestones using the HINE-2 exam. The change was approved by the FDA so that the new drug application would not rely solely on Phase 2 open label trial data. The interim analysis only included data from 78 (65%) infants who completed a 6 month assessment. The 42 subjects dropped from the analysis had died, become ventilator dependent, or withdrawn from the study before reaching their 6 month assessment date but were not identified so their characteristics could not be compared. Median age for symptom onset in the nusinersen cohort was 6.4 weeks and 8 weeks for the sham control group. The nusinersen arm had more severe baseline characteristics (earlier symptom onset, history of pneumonia, more swallowing/feeding difficulties) compared to the sham group. The interim motor function analysis included 55 patients total (39 nusinersen and 16 control) due to withdrawal of 2 patients and demise of 21 additional patients. Motor milestones were assessed using the HINE-2 assessment on days 64, 183, 302, and 394. A responder was defined as a participant who was alive and participating in the study, demonstrated at least a two-point increase in the ability to kick or a one-point increase in head control, rolling, sitting, crawling, standing, or walking. In addition, the participant had to improve in more categories than those in which he or she worsened.[16] A greater proportion of participants in the nusinersen group (n=21, 40%) than in the control group (n=0, 0%) met motor responder criteria ($p<0.0001$) at approximately six months.[16] Improvements were most common in the categories of head control, rolling, sitting, and ability to kick. Nine (18%) patients achieved full head control, 5 (10%) patients were able to independently sit, and 1 (2%) patient was able to stand.[16] At the time of the interim analysis for the intention to treat (ITT) dataset, 11/51 (21.6%) participants in the nusinersen group and 10/27 (37%) in the control group had died or required permanent ventilation (hazard ratio for event-free survival = 0.71; confidence intervals and p-values were not reported).[16] The FDA approved nusinersen based on the interim analysis which only included data from 65% of the subjects with a six month follow-up period instead of the originally planned 13 month follow-up. Based on the results of the interim analysis, the study was suspended. Because the interim analysis was of short duration (6 months), in a small number of patients (n=78), and used a different primary outcome from the original study design, the quality of the study was adversely affected. The lack of intent to treat analysis or comparison between the 78 subjects and the 43 subjects excluded from the analysis weakened the strength of randomization and introduced significant risk of selection bias. In terms of quality at this point the trial became a nonrandomized observational study. Due to attrition of 21 subjects, data was only analyzed for a total of 55 patients (n = 39 nusinersen and n= 16 control). Furthermore, the involvement of the funders in the study may have contributed an additional risk of bias. Due to high risk of selection, performance, detection, attrition and reporting bias, the study is rated as poor quality based on the Cochrane Collaboration standards for evaluating risk of bias in clinical trials.[17]

A phase 2, open-label, dose escalating study assessed safety and efficacy in patients with infantile-onset SMA type 1 (EMBRACE).[11] Subjects enrolled in the trial were between 3 weeks and 7 months old with a SNM1 homozygous gene deletion or mutation and SMA symptoms. Clinical efficacy was assessed by change in baseline of the HINE-2 and CHOP-INTEND motor function tests. The investigators powered the study to assess safety and tolerability of nusinersen, but not efficacy. Twenty patients were included in the trial and followed from 2 to 32 months. The first 4 participants received a loading dose of 6 mg on days 1, 15 and 85 followed by 12 mg on day 253 and every 4 months thereafter. The next 16 subjects received 12 mg doses on the same schedule. Follow-up visits occurred on days 16, 29, 86, 92, 169, 254, 337 and 442 and then every 4 months up to 32 months total. The data published by the investigators is an interim data analysis as the trial is currently ongoing. Improvements from baseline of 2 or more levels in at least one motor milestone were found in 13 participants including grasping (n=13), ability kick (n=9) and sitting (n=8). Change in HINE-2 score from baseline to day 92 were reported by the investigators as significant for both 6 and 12 mg dosing cohorts combined ($p=0.0002$) and for participants in the 12 mg dose group ($p<0.0001$).[11] The specific data were not reported, only the summary of the change in scores. The data for HINE-2 score changes in the 6 mg cohort were not reported. Motor function using the CHOP-INTEND score showed a mean

increase of 11.5 points (p=0.008) from baseline to 92 days with 14 out of 18 patients showing improvement on this assessment.[11] In the 12 mg cohort, 12 of 14 subjects had an increase from baseline to 92 days with a mean increase of 15.2 points. When compared to a natural history case series of infants with SMA type 1 who had a mean decline of 1.27 points per year this 15.2 point improvement in CHOP-INTEND scores was considered significant (p = 0.0013) by the investigators.[11] There were 77 serious adverse events reported in 16 participants, all considered by study investigators not related or unlikely related to the study drug, with the most common being respiratory distress or failure or respiratory infections, which are commonplace in infants with spinal muscular atrophy.[11] This study has several limitations including small sample size (n=20), open label, and short duration of follow-up (2-32 months). No information was provided on the patients that were screened but not included in the trial. No a priori definition of a clinically important change in outcome measures was established. Only 14 subjects (70%) were included in the motor outcome analysis. Finally, this study was funded by Ionis and Biogen so the investigators may have had a potential conflict of interest. For these reasons, this study is rated as poor quality using the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) assessment tool. [18]A second open label, multicenter, phase 2 trial (NURTURE) focused on the efficacy of nusinersen in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA is currently ongoing with anticipated results in 2019.

A phase 1 trial of nusinersen included 28 medically stable participants with symptomatic SMA types 2 and 3 aged 2 to 14 years.[19] Most of the participants (89%) had 3 or more copies of the SMN2 gene and a life expectancy greater than 2 years per investigator assessment. The trial was an open label, dose finding, multi-center study focused on evaluating nusinersen safety and tolerability after a single dose of medication. Exploratory efficacy outcomes included the HFMSE and Pediatric Quality of Life Inventory (PQLI). However, the study was not powered to detect statistical differences in efficacy as an a priori definition of a clinically important outcome was not stated before the start of the trial. The nusinersen doses ranged from 1 mg (n=6), 3 mg (n=6), 6 mg (n=6) or 9 mg (n =10). The pharmacokinetic assessment revealed an extended half-life of 4 to 6 months. In an increase in HFSME score by a mean of 3.1 points was observed 3 months after one 9 mg dose, although this phase 1 trial was not designed to evaluate statistical significance. No information was provided on the subjects that were screened but not included. Only 8 of the 10 patients (80%) who received a 9 mg dose were evaluated at 9-14 months. Finally, this study was funded by Ionis and Biogen. For these reasons, the study is rated as poor quality with a high risk of bias using the ROBIN-1 tool.[18] Twenty four (86%) of the participants enrolled in an extension study in which they received additional medication 9 to 14 months after the initial injection. Data from the extension trial was not reported.

Clinical Safety:

The safety profile for nusinersen is based on observations in 173 patients from the Phase 3 RCT, Phase 2 open label study in patients with symptomatic infantile onset SMA, and Phase 1 open label dose finding trial in patients with later onset SMA. Patients with SMA type 4 were not included in the preliminary trials. Due to the small number of patients included in the clinical trials and limited duration of exposure, the safety of nusinersen is not known. The most common adverse reactions that were observed in patients were lower respiratory infection (43% with nusinersen vs. 29% with placebo), upper respiratory infection (39% vs. 34%) and constipation (30% vs. 22%).[2] Thrombocytopenia developed in 6 of 56 (11%) patients after administration of nusinersen.[16] None of the 28 sham procedure patients experienced thrombocytopenia. Five of 173 (3%) nusinersen patients (3%) had a hemorrhagic complication of lumbar puncture. Proteinuria occurred in 17 of 51 (33%) nusinersen patients compared to 5/25 (20%) sham control subjects.[16] Per the manufacturer, lab testing of platelets, prothrombin time and quantitative spot urine protein testing is recommended at baseline and prior to each dose of nusinersen.[2] Repeat testing and further evaluation is recommended for urinary protein concentrations greater than 0.2 g/L.[2] The FDA review noted the following as the main safety concerns for nusinersen: thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, effects on growth, rash and possible vasculitis, and hepatic effects.[2]

In summary, nusinersen may improve motor function in infants with SMA type I as assessed by the HINE-2 or CHOP-INTEND scores within the first six months of therapy. It is not known if improvement in motor function will impact long-term survival or reliance on a ventilator. Furthermore, nusinersen is associated with serious adverse effects including thrombocytopenia and renal toxicity. Long term safety data is currently insufficient. The long term impact on survival or

ventilator dependence is not well documented due to the ongoing data collection in phase III RCTs. Evidence regarding efficacy in SMA type 2, 3 or 4 is not published. As nusinersen is the first drug FDA approved to treat SMA, there are no comparator medications. The pharmacology and pharmacokinetic properties are presented in **Table 2**. Details of the 3 trials submitted to the FDA for approval are outlined in **Table 3**. In general, the Drug Use Research Management team only evaluates randomized controlled trials in the evidence summary. However, due to the limited amount of data currently available to evaluate the safety and efficacy of nusinersen the open label Phase 1 and Phase 2 trials are also included in the evidence tables.

Look-alike/Sound-alike Error Risk Potential: No similarities noted.

Table 2. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide
Oral Bioavailability	N/A – Administered via intrathecal injection
Elimination	Urinary excretion
Half-Life	135 to 177 days in CSF and 63 to 87 days in plasma
Metabolism	Hydrolysis

Abbreviations: CSF = cerebral spinal fluid; N/A = not applicable

Table 3. Evidence Table Summarizing Nusinersen Trials Submitted to the FDA for Approval[1,11,19]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/Applicability (RCTs) Study Limitations (Observational Trials)
Chiriboga et.al. [19] OL, dose escalating, MC, Phase 1 trial	1. Nusinersen 1 mg IT x1 2. Nusinersen 3 mg IT x1 3. Nusinersen 6 mg IT x1 3. Nusinersen 9mg IT x1	Demographics Average age = 6.1 years, 39% male, 82% Caucasian, 36% were ambulatory Key Inclusion Criteria: - Patients aged 2-14 years with symptomatic SMA Type 2 and 3 and homozygous SMN1 gene deletion -Medically stable -Life expectancy ≥ 2 years Key Exclusion Criteria: -Respiratory insufficiency -Active infection -Recent hospitalization for surgery or pulmonary event within past 2 months -History of brain or spinal cord disease or bacterial meningitis -Presence of implanted CSF shunt -Significant laboratory abnormalities	ITT 1. 6 2. 6 3. 6 4. 10 (total n=28 enrolled) Attrition: Not reported	Primary Endpoint: Number of Adverse Events Pharmacokinetic Assessment: CSF half-life estimated as 132-166 days Secondary Endpoint: HFSME evaluated by physical therapist at baseline, day 29, and 85 Mean change at day 85 compared to baseline: 1. + 1.0 2. +1.0 3. +0.7 4. +3.1 Mean change at increase at 9-14 months compared to baseline 1.-1.7 2. +0.5 3. +2.5 4.+5.8 PedsQL at baseline, day 29, and day 85 No significant changes reported in any group	N/A N/A N/A	Adverse Events: Total of 89% patients reported an adverse event Adverse events (n) reported as number of events that occurred in > 2 subjects Prevalence reported as percentage of patients Most common: - Headache (n = 12 events; 39%) - Post-LP Headache (n = 7 events; 21%) - Back Pain (n = 7 events; 18%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: HIGH. No information on patients screened but not included Intervention Bias: HIGH. Open label study design, clinical meaningful changes in HFSME not determined a priori. Missing Data Bias: UNCLEAR. Attrition not reported. Reporting Bias: UNCLEAR. Funded by Ionis and Biogen. **Applicability**: Patient: Dosing finding trial in SMA Type 2 and 3 patients. Intervention: One time dosing with 4 different doses – primarily to determine safety and pharmacokinetic parameters. Only 8 patients who received the 9mg dose were evaluated at 9 to 14 months Comparator: For motor function assessment changes in function were compared to natural history cases series of SMA type 1 patients. Outcomes: Changes in motor function reported as mean changes, not individual Setting: 4 study centers in the United States: Columbia University, University of Utah, Boston Children's Hospital, and University of Texas Southwestern Medical School

Finkel, et al.[11] Phase 2, OL, dose escalating	1. Nusinersen IT at 6 mg on days 1,15, 85 and then 12 mg on day 253 and 12 mg every 4 months 2. Nusinersen 12mg IT loading doses on days 1,15, 84 and 253, then 12 mg every 4 months Duration: 32 months	Demographics: Average age at enrollment: 141 days, 60% male, 80% Caucasian -17/20 (85%) had 2 copies of SNM2 gene - 2/19 (10%) had 3 copies of SNM2 gene Key Inclusion Criteria: -Age between 3 weeks and 7 months old -SMA 1 with SMN1 gene deletion -Gestational age between 35-42 weeks -Gestational weight ≥ 2 kg -Body weight > 5th percentile Key Exclusion Criteria: -Hypoxemia -Active infection -History of brain or spinal cord disease -Presence of implanted CSF shunt -Significant laboratory abnormalities	Interim Analysis (ITT): 1. 4 2. 16 (total n=20 enrolled) Attrition: 1 infant died prior to 85 day assessment 2 patients withdrew due to infection or respiratory failure 2 patients enrolled but failed screening due to hypoxia, cardiac abnormality	Primary Endpoint: Change from baseline of HINE-Part 2 at last visit 1. (6 mg cohort): n = 1 /4 (25%) p=0.0002 2. (12 mg cohort): 15/15 (100%) p<0.0001 Secondary Endpoint: Change from baseline to last visit (92 days) in CHOP-INTEND 1. (6 mg cohort): not reported 2. (12 mg cohort): 12/14 (85%) Mean increase = 15.2 points (p=0.0013)	N/A N/A N/A N/A	Safety: Overall, 570 adverse events reports in 100% of patients. Majority of adverse events were mild (63%) or moderate (27%) in severity. Adverse events (n) reported as number of events that occurred in > 4 subjects Prevalence reported as percentage of patients Most common adverse events included: - Fever (n =14; 70%) - Respiratory Infection (n = 14; 70%) - Constipation (n=9; 45%) - Vomiting (n = 8; 40%) - Joint Contracture (n = 8; 40%) - Rash (n=5; 25%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: HIGH. No information on patients screened but not included Intervention Bias: HIGH. Open label study design. Patients and providers were not blinded. Clinical meaningful changes in HINE-2 and CHOP-INTEND not determined a priori. Missing Data Bias: HIGH. Large attrition rate; 5 patients (25%) withdrew. Reporting Bias: HIGH. Funded by Ionis and Biogen. CHOP-INTEND scores only reported for 14 patients (70%) at 92 days. **Applicability**: Patient: Patients with SMA type 1. Intervention: Multiple doses on nusinersen (6mg and 12 mg loading doses) Outcomes: CHOP-INTEND scores only reported for 14 patients (70%) at 92 days. Short follow-up duration (2-32 months) Data regarding long-term functional improvement, quality of life or other clinical outcomes is not available. Setting: Conducted in United States and Canada.

ENDEAR[1] Phase 3, MC, RCT, Sham Control	1. Nusinersen three 12 mg loading doses (day 1, 15, 29, 64), then 12 mg every 4 months IT administration (dosing scaled based on weight) n=80 2. Sham control (small needle prick on the lower back) n=41 Randomized 2:1 to nusinersen vs. sham control	Demographics: -55% female -86% Caucasian -Median age at enrollment: 175 days (range = 30 -262 days) -12/17 (71%) had 2 SMN2 gene copies -5/17 (29%) had 3 SNM2 gene copies -Median age of symptom onset 1. 6.5 weeks (range = 2-18 weeks) 2.8weeks (range = 1-20 weeks) Number of patients requiring respiratory support at baseline 1.21(26%) 2.6(15%) Key Inclusion Criteria: - Infants 7 months or younger with SMA 1 -At least 2 copies of SMN2 -Adequate nutrition and hydration with gastrostomy -Body weight ≥ 3rd percentile for age -Gestational age 37 to 42 weeks Key Exclusion Criteria: -Hypoxemia -Active infection -History of brain or spinal cord disease -Presence of CSF shunt -Significant laboratory abnormalities	Interim Evaluation: ITT: 1.80 2.41 PP (excluded patients who died or withdrew from the study): 1. 51 2. 27 Attrition: 1. 1 2. 1	Primary Endpoint: HINE-2 response*(PP population) 1.Nusinersen: 41% - Full Head Control: n= 9 (18%) - Independent Sitting: n= 5 (10%) - Standing: n=1 (2%) 2. Control: 0% Event free survival defined as time to death or permanent ventilation(original outcome) ITT Population 1. n=27 (34%) 2. n=20 (49%) HR for event free survival = 0.71 (confidence intervals not reported) Secondary Endpoint: Proportion of patients with ≥4 point increase from baseline in CHOP-INTEND (based on assessment at day 183, 302, or 394) CHOP-INTEND >4 point increase (improvement) 1. 63% 2. 3% ≥ 4 point decrease (worsening) 1. 4% 2. 40%	N/A N/A N/A N/A N/A	Outcome: Fatal adverse event 1. 12 (15%) 2. 12 (29%) Only percentages of SAEs reported, not specific numbers of events Respiratory 1. 58% 2. 63% Infections 1. 50% 2. 37% Thrombocytopenia 1. 11% 2. 0% Proteinuria 1. 33% 2. 20% Statistical significance not reported	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: HIGH. Randomization was stratified based on disease duration (≤12 weeks vs. >12 weeks). Since trial is not published, methods of randomization and concealment of allocation are not known. Nusinersen patients had earlier disease onset (6.5 weeks vs 8 weeks); more infections, respiratory/swallowing/feeding issues compared to control. Performance Bias: Sponsor, parents and key study personnel were blinded. Detection Bias: Sponsor, parents and key study personnel were blinded. Attrition Bias: HIGH. Two patients withdrew (one from each study group) and 21 patients died (nusinersen = 11 and control = 10). Reporting Bias: HIGH. Interim results are from an unblinded analysis completed by a contract research organization and reviewed by senior management team from Ionis and Biogen. Only unpublished data available. Full study results have not been evaluated or published. Primary outcome modified before interim analysis to include motor skill assessment (HINE-2 scores). Funded by Ionis and Biogen. **Applicability**: Patient: SMA type 1 patients Intervention: Doses were scale adjusted based on body weight. Comparator: Sham control Outcomes: Duration of trial = 6 months, long-term impact on survival and motor development is unknown. Setting: Conducted in multiple countries: Australia, Belgium, Canada, France, Germany, Great Britain, Italy, Japan, Korea, Spain, Sweden, Turkey and the United States

Abbreviations: CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale Expanded; HINE = Hammersmith Infant Neurological Exam; HR = hazard ratio; ITT = intention to treat; IT = Intrathecal; LP = lumbar puncture; MC = Multicenter; n = number; OL = open label; PedsQL = Pediatric Quality of Life Inventory; PP = per protocol

* Motor function improvement in HINE section 2 defined as 1) a ≥2 point increase in ability to kick, 2) ≥ 1 point increase in head control, rolling, sitting, crawling, standing or walking, and 3) improvement in more categories of motor milestones than worsening

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Appendix 1: Prescribing Information Highlights

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

SPINRAZA (nusinersen) injection, for intrathecal use
Initial U.S. Approval: 2016

——————INDICATIONS AND USAGE ——————
SPINRAZA is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (1)

——————DOSAGE AND ADMINISTRATION ——————
SPINRAZA is administered intrathecally (2.1)

Dosing Information (2.1)
- The recommended dosage is 12 mg (5 mL) per administration
- Initiate SPINRAZA treatment with 4 loading doses; the first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose; a maintenance dose should be administered once every 4 months thereafter

Important Preparation and Administration Instructions (2.2)
- Allow to warm to room temperature prior to administration
- Administer within 4 hours of removal from vial
- Prior to administration, remove 5 mL of cerebrospinal fluid
- Administer as intrathecal bolus injection over 1 to 3 minutes

Laboratory Testing and Monitoring to Assess Safety (2.3)
- At baseline and prior to each dose, obtain a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing

——————— DOSAGE FORMS AND STRENGTHS———————
Injection: 12 mg/5 mL (2.4 mg/mL) in a single-dose vial (3)

——————————— CONTRAINDICATIONS ———————————
None.

——————WARNINGS AND PRECAUTIONS ——————
- *Thrombocytopenia and Coagulation Abnormalities:* Increased risk for bleeding complications; testing required at baseline and before each dose (5.1, 2.3)
- *Renal Toxicity:* Quantitative spot urine protein testing required at baseline and prior to each dose (5.2, 2.3)

——————————— ADVERSE REACTIONS ———————————
The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection, upper respiratory infection, and constipation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

Nusinersen

Goal(s):

- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:

- Up to 6 months and up to 6 months for renewal.

Requires PA:

- Nusinersen

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. Go to # 2	
2. Is this a request for continuation of therapy?	**Yes**:Go to # 9	**No:** Go to #3
3. Was the patient's gestational age between 37 and 42 weeks?	Yes: Go to #4	No: Pass to RPh. Deny, medical appropriateness.
4. Is the patient ≤ 7 months of age at the time of the request?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
~~3.~~5. Does the patient have Spinal Muscular Atrophy (SMA) documented by genetic testing and 2 copies of the SMN2 gene?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is a baseline motor assessment available using the following functional assessment tool: Hammersmith Infant Neurological Examination (HINE-2)	Yes: Go to #7	No: Pass to RPh. Deny medical appropriateness.
7. Is the patient ventilator dependent (using at least 16 hours per day on at least 21 of the last 30 days)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #8.
~~4.~~8. Is the drug being prescribed by a neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** Approve up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
9. Has the patient's motor function improved as demonstrated by: • Improvement in baseline HINE-2 score within one month of renewal request AND • More areas of motor function improved than worsened	Yes: Approve for 6 months	No: Pass to RPh; Deny; medical appropriateness.

P&T Review: *7/1/7 (DM); 3/17 (DM)*
Implementation *4/1/17*

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OHSU Drug Effectiveness Review Project Summary Report – Deflazacort oral tablet

Date of Review: July 2017
Generic Name: deflazacort

End Date of Literature Searcy: 05/22/2017
Brand Name (Manufacturer): Emflaza™ (PTC Therapeutics)
Dossier Received: Yes

Research Questions:

1. What is the comparative efficacy or effectiveness of deflazacort compared to currently available corticosteroids in improving clinical outcomes (including improved muscle strength and mobility, prevention of long-term cardiac and pulmonary complications, and increased survival) in patients with Duchenne Muscular Dystrophy (DMD)?
2. Is deflazacort safe for treatment of DMD and what is the relative safety compared to other corticosteroids?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with deflazacort?

Conclusions:

- The report conducted by the Drug Effectiveness Review Project (DERP) evaluated deflazacort for the treatment of DMD based on 4 randomized controlled trials (RCT), 3 systematic reviews, and one guideline.
- 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.
- Similarly, there is a lack of quality evidence evaluating comparative differences in adverse effects between deflazacort and prednisone. Evidence that deflazacort is associated with significantly less weight gain (mean difference [MD] 2.91 to 4.1 kg) but more cataracts than prednisone was of insufficient quality. 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. Two of these RCTs were completed more than 20 years ago, and only one included patients in the United States. As a result, these data may not be applicable to patients under the Oregon Health Plan (OHP) today. There was no comparative evidence of deflazacort and prednisone beyond 2 years of follow-up.
- There is insufficient evidence to evaluate differences between deflazacort and other corticosteroids for DMD or other conditions.
- Overall, there is insufficient evidence to evaluate differences in adverse effects between deflazacort and other oral corticosteroids. Evidence is limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients.

Recommendations:

- Implement prior authorization criteria that restricts use to patients with DMD and documented contraindication or serious intolerance to oral corticosteroids (**Appendix 3**).

- Refer deflazacort to the Health Evidence Resource Commission (HERC) for funding placement as a drug with high cost and marginal benefit compared to currently available low-cost oral corticosteroids.

Background:
Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 7250 males between the ages of 5 to 24 years.[1] Currently, in the Oregon Health Plan (OHP) population, approximately 70 fee-for-service patients and more than 300 patients enrolled in coordinated care organizations have a diagnosis of muscular dystrophy. Available claims data for OHP are unable to distinguish between patients with various types of muscular dystrophy. Based on the estimated prevalence of DMD, approximately 60 OHP patients with muscular dystrophy may be eligible for this medication. Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death before the age of 20.[2] Only 25% of patients remain ambulatory by age 16.[3] There is currently no curative treatment, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology recommend either deflazacort or prednisone as first-line treatment in children over 5 years of age to improve muscle and pulmonary function and reduce risk of scoliosis.[2] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs. 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]

Deflazacort is a corticosteroid which has been on the market in Europe and other countries for decades, but only recently achieved FDA approval in the United States. Deflazacort was approved through the FDA priority review process for the treatment of DMD in patients age 5 years and older based on the results of 2 randomized active-comparator trials including 196 and 18 patients each. The primary outcome evaluated change in muscle strength measured by a modified Medical Research Council scale. The Medical Research Council scale (MRC) ranges from 0 to 10 points, with higher scores indicating greater strength. A score of 10 indicates the muscle is able to contract against full resistance and 0 represents no movement observed.[1] Scores are typically assessed and summarized for several muscle groups in several positions (sitting, prone, supine, and lying on the side). The minimum clinically important difference with this scale has not been established. Other studies evaluated change in muscle function using timed function tests such as the time required to stand from a supine position or the time required to walk a certain distance. Other methods to evaluate functional improvement included use of the Motor Function Index which evaluates a patient's ability to climb four 17 cm stairs, stand from a sitting position, and walk 10 meters on flat ground.[5] Each test is evaluated on a 1-3 scale indicating if individuals are able to complete the task without assistance (1 point), accomplish the task with assistance (2 points), or are not able to complete the task (3 points).[5] Total scores range from 3 to 9 with larger scores indicating more severe disease.[5] The validity of this scale and minimum clinically important change has not been determined.

Deflazacort has also been studied for treatment on multiple conditions including idiopathic thrombocytic purpura, essential mixed cryoglobulinemia, juvenile chronic arthritis, nephrotic syndrome, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, solid organ transplant rejection, and urolithiasis.[4] Randomized controlled trials have examined the efficacy or safety of deflazacort compared to other corticosteroids. However, long-term population-based studies indicate that oral prednisone may be associated with greater incidence of weight gain, hirsutism and cushingoid appearance, while deflazacort may have greater risk of cataracts.[1,6,7] The DERP review summarizes comparative evidence of deflazacort versus other corticosteroids for the treatment of DMD. Evidence for other potential off-label conditions will also be considered in this report.

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

Methods:
An April 2017 Drug Effectiveness Review Project (DERP) report compared deflazacort to prednisone for children with Duchenne Muscular Dystrophy was used to inform recommendations for this drug evaluation. The DERP report was supplemented with information from the manufacturer's prescribing information and the FDA website. In addition, new evidence published since completion of the DERP report that evaluated use for FDA-approved indications or off-label conditions was identified. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The DERP is part of the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. 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. The original DERP report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

Summary Findings: Duchenne Muscular Dystrophy
A total of 4 RCTs, 3 systematic reviews, and one guideline were identified in the DERP report. All trials included a similar population of patients (males at least age 5 with DMD), and all compared FDA-approved dosing of deflazacort 0.9 mg/kg/day to prednisone 0.75 mg/kg/day.[2] Overall evidence from these trials was graded as poor quality due to significant methodological flaws and lack of reported data.[2]

The primary study used for FDA approval included 196 males from the United States and Canada randomized to deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo.[2] At 12 weeks, patients in the placebo group were re-randomized to a treatment arm. The trial was completed in 1995, and at this time the distinction between types of muscular dystrophy was not well defined. As a result, this trial included patients with either Duchenne or Becker muscular dystrophy limiting applicability to patients with DMD today. The primary outcome was change in muscle strength at 12 weeks measured using a modified MRC index score.[1] Scores are based on several muscle strength assessments and evaluated on a 0 to 10 point rating scale with lower scores indicating more severe disease.[1,8] Secondary outcomes included muscle strength at 1 year, motor function, pulmonary function, disease severity, adverse effects, weight gain and change in growth. Outcomes are summarized in **Table 1**. Actual MRC scores at baseline, 12 weeks and 1 year were not reported and numbers represent the change in MRC score from baseline. Overall, there was no significant difference in muscle strength between patients treated with either corticosteroid at 12 weeks or 1 year.[2] Compared to placebo at 12 weeks, these differences in MRC were statistically significant for both groups, though the clinical significance of 0.25 to 0.38 points is questionable.[8] There was no difference between deflazacort and prednisone in timed motor function tests between groups at 1 year.[2] Timed motor function tests included time to stand from a supine position, climb 4 stairs, run or walk 30 feet, or propel a wheelchair 30 feet.[2] This evidence had several important limitations which decrease confidence in these results including potential conflicts of interest and lack of information on randomization methods, allocation concealment, and baseline disease severity between groups.

Table 1. Mean change in MRC Score^ from Baseline (95% CI).[8]

	12 weeks	1 year
Placebo	-0.1 (-0.23 to 0.03)	-
Deflazacort 0.9 mg/kg	0.15 (0.01 to 0.28)*	0.39 (0.25 to 0.54)
Deflazacort 1.2 mg/kg	0.26 (0.12 to 0.40)*	0.38 (0.23 to 0.54)
Prednisone 0.75 mg/kg	0.27 (0.13 to 0.41)*	0.23 (0.07 to 0.38)

*Statistically different from placebo.
^MRC score was evaluated on a 0 to 10 point scale.

A second trial of 100 German patients also evaluated the comparative efficacy and safety of prednisone and deflazacort.[2] Overall, data from this study were rated as poor quality due to significant methodological flaws and lack of reported data. Preliminary results of this RCT including 67 patients were published in 1995 and final results including all 100 patients were available in an unpublished conference report in 2000.[2] Of the 100 patients enrolled, 80% remained in the trial at 2 years.[2] Overall, there was no difference in muscle function or strength between groups. However, numerical data for these outcomes were not reported, and results from this trial were limited by highly disparate attrition rates between groups without use of an intention-to-treat analysis.[2]

The third RCT was double-blinded and included 18 Italian patients followed for 2 years.[2] Patients were randomized to prednisone or deflazacort and reportedly stratified by disease severity and age.[2] However, methods used for randomization and allocation concealment were unclear.[2] Outcomes reported at 1 and 2 years included muscle strength, motor outcomes (reported descriptively) and weight gain. No difference was observed in muscle strength or functional scores at 2 years.[2] This study was significantly limited by the small sample size, lack of reported outcomes, and significant risk of bias.[2]

Another RCT evaluated 34 Iranian patients randomized to deflazacort or prednisone.[2] The study was limited by poor reporting of methodological methods including methods of randomization, allocation concealment, blinding, and baseline characteristics for each group.[2] In addition, a significant portion of patients were lost to follow up with high differential rates between groups (17.6% in deflazacort vs. 29.4% in prednisone group) increasing risk of bias.[2] The efficacy outcomes evaluated included change in the motor function index (**Table 2**) up to 18 months. The motor function index evaluates functional status on a 7-point scale (range 3-9) with larger scores indicating more severe disease.[5] At 12 months, patients treated with deflazacort had a statistically significant increase from baseline in the mean motor function index compared to prednisone, but differences failed to achieve statistical significance at 18 months.[2,5]

Table 2. Motor function index reported as mean score (95% CI) and mean difference (MD) from baseline.[5]

	Baseline	12 months	18 months
Deflazacort 0.9 mg/kg	4.93 (95% CI 4.4 to 5.5)	4.36 (95% CI 3.7 to 5.0); MD -0.57	4.64 (95% CI 3.8 to 5.5); MD -0.29
Prednisone 0.75 mg/kg	5.0 (95% CI 4.6 to 5.5)	5.25 (95% CI 4.4 to 6.1); MD 0.25	5.75 (95% CI 4.4 to 7.2); MD 0.75
Mean difference between groups		0.82; p=0.001	1.04; p=0.128

Three systematic reviews also evaluated comparative efficacy and safety between prednisone and deflazacort.[2] Though the RCTs included in these reviews differed, they all reached similar conclusions. Evidence for motor outcomes was graded as insufficient to very low quality demonstrating no difference in efficacy between deflazacort and prednisone.[2]

One guideline from the American Academy of Neurology on use of corticosteroids for treatment of DMD was included in the DERP report. Evidence supporting recommendations in this guideline included one RCT and multiple observational studies that evaluated the comparative effectiveness of deflazacort and prednisone.[2] The majority of observational evidence included cohort or case-control studies with a defined control group, masked outcome assessment, and description of potential confounding factors.[9] Overall, evidence was graded as moderate quality indicating moderate assessment of benefit versus risk, low quality indicating small benefit relative to risk, or very low quality indicating there is insufficient evidence to evaluate risk versus benefit. Due to limitations in the evidence, many recommendations are graded as low quality.[2] No specific recommendations are made for any particular agent. Evidence supporting use of prednisone to improve strength and pulmonary function was rated as moderate quality.[2] There was low quality evidence to support use of deflazacort to improve strength and pulmonary function, delay loss of ambulation by 1.4 to 2.5 years, and increase survival at 5 or 15 years.[2] Evidence regarding survival was primarily derived from 3 observational studies which demonstrated increased mortality in untreated patients (21-43%) compared to those treated with deflazacort (3-11%).[6] Six observational studies evaluated outcomes of muscle strength and ambulation with deflazacort treatment and demonstrated improvements in motor outcomes using various measures.[6] In 3 of these studies, the age at which patients lost ambulation was improved by 1.4 to 2.5 years in patients treated with deflazacort compared to no treatment.[6] Two additional studies evaluating both prednisone and deflazacort demonstrated improvements in age at loss of ambulation for both medications.[6] Evidence evaluating the need for scoliosis surgery, delaying the onset of cardiomyopathy, and improving timed motor function tests was evaluated as low quality for both prednisone and deflazacort.[2] Similarly, there was low quality evidence that deflazacort and prednisone provide similar improvements in motor function, and low quality evidence that deflazacort has less weight gain but greater risk for cataracts than prednisone.[2] Direct comparative evidence included 2 observational studies that demonstrated no difference in functional motor outcomes over 1 year and 5.49 years each.[6] In these studies, weight gain was more common in the first year of treatment (mean weight increase of 21.3% with prednisone vs. 9% with deflazacort) corresponding to a mean weight increase at 1 year of 5.08 kg in patients treated with prednisone compared to 2.17 kg in patients treated with deflazacort ($p<0.05$).[6] However, one study noted no difference in weight in older children (12-15 years).[6] Cataracts occurred more often in patients treated with deflazacort compared to prednisone, though results were not statistically significant.[6] There was insufficient evidence to compare differences between therapies for other outcomes including pulmonary and cardiac function.[2]

Evidence evaluating adverse effects was also reported from these 4 RCTs. In the primary study used for FDA approval (n=196), patients randomized to deflazacort had less weight gain (5.05 kg) compared to prednisone (8.45 kg; MD 3.4 kg; $p<0.0001$) over the course of 1 year. However, incidence of cataracts was higher with deflazacort (6.6%) at 1 year compared to prednisone (4.4%; p-value not reported).[2] Similar trends were noted between groups with evaluation of body mass index.[2] Similarly in subsequent studies, patients treated with prednisone versus deflazacort reported higher incidence of weight gain leading to treatment discontinuation (data not reported) and more weight gain at 1 and 2 years (2.17 kg vs. 5.08 kg, p-value not reported and 4.6 kg vs. 8.7 kg; $p<0.05$, respectively). Another study reported that patients treated with prednisone had a greater mean percent increase in weight than patients treated with deflazacort at 12 months (21.7% vs. 13.0%; $p=0.001$) and 18 months (32% vs. 21.7%; $p=0.046$) corresponding to a mean 2.41 to 3.18 kg weight increase in patients treated with prednisone compared to deflazacort.[2,5] One other study (n=100) also reported that more patients on deflazacort developed cataracts compared to patients treated with prednisone (36% vs. 3%, p-value not reported).[2] However, evidence from these RCTs was limited by inadequate or unclear methods, lack of adequately reported data, and high and/or disparate attrition rates without use of intention-to-treat analyses.[2] Systematic reviews evaluating adverse effects of deflazacort and prednisone also concluded that deflazacort was associated with less weight gain than prednisone though evidence was graded as very low quality indicating very little confidence in the estimated effect.[2] Further studies are needed to evaluate comparative safety and adverse effects between deflazacort and other corticosteroids.

Because deflazacort is a corticosteroid, FDA labelling includes warnings and precautions for adverse effects which have been associated with corticosteroid use. Warnings are summarized in **Appendix 1**. Additional rare but serious adverse effects include effects on growth and development, myopathy, Kaposi's sarcoma, thrombotic events, and anaphylaxis.[10] Deflazacort suspension also includes benzyl alcohol preservative which has been associated with increased risk of serious and fatal reactions in infants and is not approved in children less than 5 years of age.[10] Common adverse effects (occurring in >10% of patients compared to placebo at 12 weeks) included cushingoid appearance, weight gain, and increased appetite.[10] Because clinical trials included a limited population of patients randomized to deflazacort and placebo (n=51 and 50), rates of adverse events may not be reflective of rates observed in clinical practice.[10]

Off-label Indications

A high-quality systematic review published in 2012 examined the comparative efficacy and safety of deflazacort versus other corticosteroids for the treatment of nephrotic syndrome.[11] The review included 3 single-center RCTs (n=91 patients total) in France, Denmark and Argentina.[11] Patients were randomized to deflazacort or prednisone in 2 studies and to deflazacort or methylprednisolone in the third study.[11] Two trials evaluated use in children and one evaluated adults with newly diagnosed nephrotic syndrome. Data for these trials were described descriptively as they did not consistently report similar outcomes and evaluated different populations. Two studies examine time to remission, with no apparent difference between patients randomized to deflazacort or another corticosteroid.[11] In 1 study, the mean number of new relapses and the proportion of children who were relapse free at 1 year was improved with treatment of deflazacort compared to prednisone (MD 1.9; 0.9 vs. 2.8; $p<0.002$ and 60% vs. 10%; $p=0.002$, respectively).[11] Another study reported no difference in the number of relapses after more than 4 years of follow-up.[11] No significant difference was observed in mean growth velocity, fasting blood sugar, infection rate, or cushingoid symptoms when deflazacort was compared to other corticosteroids.[11] One study did report a smaller mean decrease with deflazacort compared to prednisone in bone density (3.6 vs. 5.9 gHa; $p<0.05$) and bone mineral content (0.0050 vs. 0.0089 gHa/cm^2/month; $p<0.05$) of the spine, while another study failed to achieve statistical significance between groups.[11] Evidence was limited by lack of defined primary and secondary outcomes and small patient population.[11] In addition, one trial failed to report adequate randomization methods, and in another, providers and outcome assessors were not blinded, increasing risk of bias.[11]

Randomized Controlled Trials:

A total of 155 citations were manually reviewed from the initial literature search. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. After further review, 139 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), population (eg, healthy subjects), or outcome (eg, non-clinical). Several excluded trials examined effects on bone mineral density or content. However, bone mineral density can vary between instruments and trials did not report outcomes using standardized methods (i.e. T-score or Z-score) making interpretation of these outcomes difficult. The remaining 20 trials were critically evaluated for internal validity and risk of bias. Seven trials were excluded due to substantial flaws and lack of reported methods which significantly increase risk for selection bias (i.e. methods of randomization and allocation concealment, inclusion and exclusion criteria, and relevant baseline characteristics were not reported), and results should not be considered in the decision-making process. Results of the remaining trials which evaluate evidence for deflazacort in off-label conditions are summarized in the table below. Overall, evidence is limited by small population size, significant methodological flaws, and lack of reported outcomes which increases risk of bias. In addition, the majority of studies were completed outside the United States at a single medical center, and published more than 15 years ago limiting applicability to the OHP population today.

Table 3. Description of Comparative Clinical Trials.

Study/Location	Comparison	Population/ Location	Primary Outcome	Results	Study Limitations and Potential Sources of Bias
Grosso S, et al. 2008.[12] OL, RCT N=35 Duration: 6 months	1. Hydrocortisone daily and tapered at monthly intervals on the following schedule: 10 mg/kg, 5 mg/kg, 2.5 mg/kg, 1 mg/kg, and 1 mg/kg on alternate days, thereafter 2. Deflazacort 0.75 mg/kg	Children with drug-resistant epilepsy Italy	Proportion of patients with >50% decreased seizure frequency at 6 months	1. 44% 2. 47% P=0.9	Patients and providers were not blinded and patients were allocated to groups on an alternate basis at hospitalization increasing risk of bias. Allocation concealment was not reported.
Elli A, et al. 1993.[13] Single-center, OL, RCT N=50 Duration: 1 yr	1. Deflazacort 2. Methylprednisolone Dosing administered in a ratio of 6 mg deflazacort to 4 mg methylprednisolone. Dose was tapered to 12 or 18 mg at 12 months.	Kidney transplant patients Italy	No primary outcome specified. Clinical outcomes included rejection episodes and weight gain at 1 year	Acute rejection episodes 1. 9 (36%) 2. 11 (44%) p-value NS Mean change in weight 1. 1.25 kg 2. 2.8 kg P<0.05	Inclusion and exclusion criteria were not specified. Randomization and allocation concealment methods were unclear. Baseline weight was higher in patients treated with methylprednisolone (2.7kg). Open-label study increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of reporting bias.
Kim Y, et al. 1997.[14] OL, single-site, RCT N=82	1. Deflazacort 2. Prednisolone Dose given in a ratio of 1 mg to 1.2 mg of prednisone to deflazacort	Kidney transplant patients with pre- or post-transplant DM Korea	No primary outcome specified. Outcomes included change in body weight, insulin requirements, acute rejection, adverse effects	50% dose reduction of insulin or diabetic agents 1. 12 (30.8%) 2. 2 (5%) P=0.023 Weight 1. 1.74 kg weight loss 2. 0.58 kg weight loss	Randomization and allocation concealment, methods were unclear. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias.
Ferraris JR, et al. 2007.[15] OL, MC, RCT N=31 Duration: 3 yrs	1. Deflazacort 0.3 mg/kg/day 2. Methylprednisolone 0.2 mg/kg/day	Children following kidney transplantation (mean time since transplantation was 2.1 years) Argentina	No primary outcome specified. Outcomes included rates of adverse effects compared to baseline (growth, body weight, BMD, and effects on	No specified primary outcome. Multiple outcomes described descriptively. BMI was not significantly different between groups. More patients treated with deflazacort had an LDL<100 mg/dL (p<0.001) and normal	Randomization and allocation concealment methods were unclear. Patients and providers were not blinded increasing risk of bias. Primary and secondary outcomes were not pre-specified and were evaluated post-hoc. Adverse effects were evaluated using multiple analyses increasing risk of reporting bias. Multiple outcomes were described descriptively. Use of concomitant lipid or glucose-lowering therapies was not

			glucose and lipid metabolism).	glucose/insulin ratio (p=0.02) at 2 or 3 years.	addressed. Four patients (13%) were withdrawn from the study due to onset of puberty.
Saviola GL, et al. 2007.[16] Single-center, OL, cross-over, RCT N=21 Duration: 1 yr	1. Deflazacort 7.5 mg/day 2. Methylprednisolone 4 mg/day At 6 months, patients were allocated to the alternate treatment group	Adults with active RA or psoriatic arthritis, naïve to steroid treatment Italy	No specified primary outcomes. Efficacy was evaluated using ACR score at 6 and 12 months.	ACR50 at 6 months 1. 5/9 (55.5%) 2. 6/11 (54.5%) p-value NR ACR50 at 12 months 1. 6/9 (66.7%) 2. 7/11 (63.6%) p-value NR	Randomization and allocation concealment methods not stated. Patients and providers were not blinded increasing risk of bias. Primary and secondary outcomes were not specified.
Messina O, et al. 1992.[17] DB, RCT N=16 Duration: 1 yr	1. Deflazacort 12 mg/day 2. Prednisone 10 mg/day	Patients with RA Argentina	No primary outcome specified. Clinical outcomes included change in joint involvement, morning stiffness, and physical activity 12 months.	Changes in joint involvement, and morning stiffness NR. Change in physical activity was NS (described descriptively).	Blinding performed with identical capsules. Randomization generated with use of a computer with allocation concealment. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study not powered to determine differences in outcomes.
Loftus J, et al. 1991.[18] DB, RCT N=34 Duration: 1 yr	1. Deflazacort (mean dose 9.07 mg/day) 2. Prednisone (mean dose 7.87 mg/day) Corticosteroids administered as alternate-day regimens and in a 1.2 to 1 mg ratio of deflazacort to prednisone	Children with chronic juvenile rheumatoid arthritis England	No primary outcome specified. Outcomes included joint count, height, weight, and fractures.	No specified primary outcome. No statistical difference was noted in joint count, height, or fractures. Weight gain at 1 year was greater for prednisone than deflazacort; p<0.02 (described descriptively)	Randomization and blinding methods were not reported. Baseline weight was not reported. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study was not powered to determine differences in outcomes. Data on weight outcomes was not reported.
Gray R, et al. 1991.[19] Blinded, RCT N=26	1. Deflazacort 2. Prednisone Dose was fixed for first 15 days then adjusted based on clinical requirements	Adults with RA, polymyalgia rheumatic, mixed connective tissue disease, or severe eczema	No primary outcome specified. Clinical outcomes included weight, early morning stiffness, grip strength, pain and functional	No primary outcome specified. No statistically significant differences were observed between treatment groups for all clinical outcomes.	Randomization and allocation concealment methods were not reported. Patients blinded using identically packaged medications. Blinding of providers unclear. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study was

Duration: 3 months			assessments, and adverse effects		not powered to determine differences in outcomes. More patients in the deflazacort group began additional immunotherapy at the start of the study.
Di Munno O, et al. 1995.[20] Cross-over, DB, RCT N=31 Duration: 12 weeks	1. Deflazacort 24 mg daily 2. Deflazacort 48 mg on alternate days 3. Methylprednisolone 16 mg daily 4. Methylprednisolone 32 mg on alternate days After 2 weeks, dose was titrated based on clinical response. At 6 weeks patients were allocated to the alternate dosing regimen (daily vs. alternate day).	Polymyalgia rheumatica	No primary outcome specified. Clinical outcomes included pain scores (evaluated by visual analogue scale) and morning stiffness	Mean pain scores 1. -4.5 2. -4.6 3. -6.3 4. -6.0 p-values NS between all Mean change in morning stiffness from baseline (minutes) 1. -83 2. -84 3. -132 4. -116	Randomization and allocation concealment methods were unclear. Blinding achieved with use of identical packaging though tablets had different appearances. 7 patients (23%) were excluded from the analysis. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of reporting bias.
Eberhardt R, et al. 1994.[21] DB, MC, RCT N=76 Duration: 12 months	1. Deflazacort 2. Prednisone Mean daily dose was 8.5 mg deflazacort and 7.3 mg prednisone.	Patients with RA Germany	Ritchie Index (an evaluation of 53 joint groups each scored on a 0-3 scale; total range: 0 to 159)	Ritchie index at 12 months (SD) 1. 12.8 (7.46) 2. 9.8 (7.6) P=0.4954	Randomization, allocation concealment, and blinding methods were unclear. Concomitant use of other medications for RA and baseline disease severity were not reported. 23 patients (30%) were lost to follow-up.
Lund B, et al. 1987.[22] DB, cross-over, RCT N=30	1. Deflazacort 2. Prednisone Dosing administered in a ratio of 1.2-1.8 mg deflazacort to 1 mg prednisone for 2 week periods	Patients with polymyalgia rheumatic Denmark	Disease activity, pain and tenderness evaluated using a visual analog scale	Results described descriptively. No difference was observed in general disease activity, pain or tenderness.	Randomization methods were unclear and baseline disease severity for each group was not reported. Multiple analyses performed without methods to control for multiplicity. Study not powered to determine differences in outcomes.
Rizzato G, et al. 1997.[23] OL, RCT	1. Deflazacort 2. Prednisone	Patients with chronic pulmonary sarcoidosis	No primary outcome specified. Clinical outcomes	Fractures 1. 1/28 (3.5%) 2. 5/30 (16.7%) p-value NR	Randomization and allocation concealment methods were unclear. Disease duration was longer for patients treated with deflazacort (5.6 vs. 3.5 years). Dose and duration of

N=72 Mean duration: 42 months	Mean starting dose was 22 mg for each group and tapered based on clinical requirements		included fracture events		treatment were not equivalent. Open-label trial further increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Bone toxicity analysis only reported in 58 patients (80%).
Ferrari A, et al. 1991.[24] OL, RCT N=27 Duration: 24 weeks	1. Deflazacort 1.4 mg/kg/day 2. Prednisone 1 mg/kg/day Treatment was tapered upon complete response to treatment (platelet count >150) or completion of 4 weeks of treatment	Autoimmune thrombocytopenic purpura	No primary outcome specified. Clinical efficacy outcomes included complete response (platelet count >150) and no response (platelet count <50) after 24 weeks	Complete response 1. 2/11 (18%) 2. 2/12 (17%) No treatment response 1. 4/11 (36%) 2. 4/12 (33%) p-values NS	Randomization and allocation concealment methods were unclear. Open label design increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Four patients (14.8%) were excluded increasing risk of attrition bias. Study was not powered to determine differences in outcomes.

Abbreviations: ACR50 = 50% improvement in the American College of Rheumatology criteria; BMD = bone mineral density; BMI = bod mass index; DMD = Duchenne Muscular Dystrophy; DXA = dual x-ray absorptiometry; ESRD = end-stage renal disease; MC = multicenter; MD = mean difference; NR = not reported; NS = not significant; OL = open-label; RA = rheumatoid arthritis; RCT = randomized clinical trial; SD = standard deviation; yrs = years.

Table 1. Pharmacology and Pharmacokinetic Properties.[1,10]

Parameter	
Mechanism of Action	Corticosteroid prodrug which has anti-inflammatory and immunosuppressant properties. The exact mechanism in patients with Duchenne muscular dystrophy is unclear.
Oral Bioavailability	Not reported; area under the curve is unchanged upon administration with food
Distribution and Protein Binding	Protein binding = 40% Exact volume of distribution is unknown
Elimination	68% excreted unchanged in urine 18% metabolized
Half-Life	Half-life of approximately 1.17 to 2.4 hours. Elimination is almost complete by 24 hours after a single dose.
Metabolism	Converted to the active metabolite, 21-des-deflazacort by esterase Metabolized via CYP3A4 and p-glycoprotein

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Appendix 1: Prescribing Information Highlights

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

EMFLAZA (deflazacort) tablets, for oral use
EMFLAZA (deflazacort) oral suspension
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
EMFLAZA is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended once-daily dosage is approximately 0.9 mg/kg/day administered orally (2.1)
- Discontinue gradually when administered for more than a few days (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg (3)
- Oral Suspension: 22.75 mg/mL (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to deflazacort or any of the inactive ingredients in EMFLAZA (4)

----------WARNINGS AND PRECAUTIONS----------
- *Alterations in Endocrine Function*: Hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, and hyperglycemia can occur; Monitor patients for these conditions with chronic use of EMFLAZA (2.2, 5.1)
- *Immunosuppression and Increased Risk of Infection:* Increased risk of new, exacerbation, dissemination, or reactivation of latent infections, which can be severe and at times fatal; Signs and symptoms of infection may be masked (5.2)
- *Alterations in Cardiovascular/Renal Function:* Monitor for elevated blood pressure and sodium, and for decreased potassium levels (5.3)
- *Gastrointestinal Perforation:* Increased risk in patients with certain GI disorders; Signs and symptoms may be masked (5.4)
- *Behavioral and Mood Disturbances:* May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis (5.5)
- *Effects on Bones:* Monitor for decreases in bone mineral density with chronic use of EMFLAZA (5.6)
- *Ophthalmic Effects*: May include cataracts, infections, and glaucoma; Monitor intraocular pressure if EMFLAZA is continued for more than 6 weeks (5.7)
- *Vaccination:* Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids (5.8)
- *Serious Skin Rashes:* Discontinue at the first sign of rash, unless the rash is clearly not drug related (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 10% for EMFLAZA and greater than placebo) are Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis (6.1)

----------DRUG INTERACTIONS----------
- Moderate or strong CYP3A4 inhibitors: Give one third of the recommended dosage of EMFLAZA (7.1)
- Avoid use of moderate or strong CYP3A4 inducers with EMFLAZA, as they may reduce efficacy (7.1)

To report SUSPECTED ADVERSE REACTIONS, contact Marathon Pharmaceuticals, LLC at 1-866-562-4620 or DrugSafety@propharmagroup.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 02/2017

Appendix 2: Literature search

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1	deflazacort.mp.	527
2	limit 1 to (english language and humans)	377
3	limit 2 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 meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	155

Appendix 3. Proposed Prior Authorization Criteria

Drugs for Duchenne Muscular Dystrophy

Goal(s):

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

Length of Authorization:

- 6 months

Requires PA:

- Eteplirsen
- Deflazacort

Covered Alternatives:

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

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

Approval Criteria		
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Eteplirsen and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for continuation of eteplirsen treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
4. Is the patient ≥ 5 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort or other corticosteroids?	**Yes:** Approve for up to 6 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of another oral corticosteroid.
7. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: • Deletion of exons 45 to 50 • Deletion of exons 48 to 50 • Deletion of exons 49 and 50 • Deletion of exon 50 OR • Deletion of exon 52?	**Yes:** Go to #8 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
8. Has the patient been on a stable dose of corticosteroid for at least 6 months?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the patient ambulatory with a 6-minute walk distance greater than 200 meters?	**Yes:** Document baseline 6-minute walk distance and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Does the patient remain ambulatory?	**Yes:** Go to #2	**No:** Pass to RPh, Deny; medical appropriateness.
2. Has the patient maintained baseline functional level as evaluated by the following criteria: • 6-minute walking distance greater than baseline OR • 6-minute walking distance which has not declined by more than 30 meters or 10% of baseline, whichever is less?	**Yes:** Approve for up to 6 months Document functional status.	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *07/17 (SS)*
Implementation: *TBD*

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

New Drug Evaluation: Eteplirsen injection, intravenous

Date of Review: July 2017
Generic Name: eteplirsen injection

End Date of Literature Search: 06/02/2017
Brand Name (Manufacturer): Exondys 51 (Sarepta Therapeutics, Inc.)
Dossier Received: Yes

Research Questions:

1. What is the efficacy of eteplirsen compared to placebo or currently available treatments of Duchenne Muscular Dystrophy (DMD)?
2. Is eteplirsen safe for treatment of DMD?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with eteplirsen?

Conclusions:

- Efficacy of eteplirsen for DMD remains to be established. Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes do not correlate with any clinical improvement. Additionally, there are significant methodological concerns and a high risk of bias in available studies.
- There is insufficient evidence that eteplirsen treatment in patients with DMD is associated with any clinical change in symptoms or functional status. Functional improvement was primarily evaluated using the 6-minute walk test (6MWT). In a single study of 12 patients, no difference was observed between patients treated with eteplirsen and placebo in the 6MWT at 24 or 48 weeks.[1] A long-term extension study evaluating functional improvement assessed with the 6MWT or North Star Ambulatory Assessment (NSAA) over 36 months compared eteplirsen to a historical control group.[2] However, significant limitations associated with this study including differing baseline characteristics between groups, inability to control for potential confounders, and differences in assessment methods limit confidence in these results. Labeling for eteplirsen specifies that a clinical benefit has not been established.[3]
- Eteplirsen was primarily evaluated in 2 studies (n=24) which examined change in the level of dystrophin protein. After 3.5 years of treatment, patients treated with eteplirsen had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] Change in dystrophin protein level has not been validated as a surrogate outcome in DMD and there is no evidence to support it is correlated to clinical outcomes. The minimum change in dystrophin level which may result in a clinical improvement has not been established.
- There is insufficient evidence to evaluate safety of eteplirsen for treatment of DMD. The safety population included a total of 114 patients treated with at least one dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Serious adverse events occurred in 6 patients (5.3%) and were consistent with expected events for a population of patients with DMD.[1]
- There is insufficient evidence to evaluate differences in specific populations or subgroups.

Recommendations:

- Recommend implementation of prior authorization criteria limiting use to the population studied and requiring maintained functional status with continuation of therapy (**Appendix 2**).
- Due to the lack of evidence supporting clinical efficacy of eteplirsen for the treatment of Duchenne muscular dystrophy, consider referral of eteplirsen to the Health Evidence Resource Commission (HERC) for funding placement as a medication with high cost and no clinically meaningful benefit.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder which results in the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 5000 to 7250 patients age 5 to 24 years.[1,4] Currently, in the Oregon Health Plan (OHP) population, approximately 70 fee-for-service patients and more than 300 patients enrolled in coordinated care organizations have a diagnosis of muscular dystrophy. Available claims data for OHP is unable to distinguish between patients with various types of muscular dystrophy. Based on this data and the estimated prevalence of mutations amenable to exon 51 skipping, approximately 3-4 OHP patients may be eligible for this medication. Without a functional dystrophin protein, muscle fibers degenerate and are eventually replaced with adipose and fibrotic tissue.[1] Patients with DMD experience progressive muscle deterioration leading to pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications lead to wheelchair dependence between the ages of 8-16 and death before the age of 20.[1,5] Only 25% of patients remain ambulatory by age 16.[1] There is currently no curative treatment, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression.[4] Guidelines from the American Academy of Neurology recommend glucocorticoids as first-line treatment in children over 5 years of age to improve muscle and pulmonary function and reduce risk of scoliosis.[5] 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]

Recently the FDA approved eteplirsen, an oligonucleotide indicated for patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[3] In approximately 13% of patients with DMD, exon 51 is included in pre-mRNA and one or more nearby exons are deleted.[1] This results in a shift in the reading-frame as the protein is formed and leads to reduction or absence of dystrophin protein. Eteplirsen binds to exon 51 of dystrophin pre-mRNA leading to exclusion of this exon, partially restoring the reading-frame, and forming a potentially functional, truncated dystrophin protein. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[1] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[1] It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes. Similarly, the minimum change in dystrophin level which may result in a clinical improvement has not been established. Some experts suggest that very minimal improvements may constitute a beneficial change in dystrophin level while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[1,6] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[1]

Efficacy outcomes which are clinically important in patients with DMD include muscle strength, functional status, quality of life, disease progression, and mortality. Functional improvement is often evaluated using the 6-minute walk test (6MWT) and the North Star Ambulatory Assessment (NSAA) score. The 6MWT evaluates the distance a patient is able to walk in 6 minutes and evaluates both function and endurance.[7] 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.[2,8,9] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[7] The NSAA evaluates 17 functional activities including standing, walking, standing up from a chair, standing on 1 leg, climbing/descending step, moving from lying to sitting, rising from the floor, jumping, hopping,

and running.[1] Each item is evaluated on a 3 point scale with a total score ranging from 0 to 34. 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.[10] The NSAA is considered a more comprehensive measure of functional status compared to other functional assessments, but score is often very dependent on patient effort.[1] The minimum clinically important difference in NSAA score has not been determined. Other functional assessments include timed measures of rising from a sitting or supine position, 10-meter run/walking time, or time to climb 4 stairs.[7]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Eteplirsen was evaluated in 3 poor quality studies with significant flaws (1 randomized placebo controlled trial and 2 open-label studies). All patients in these trials were ambulatory and on a stable dose of corticosteroids for at least 6 months. Study 1 was a double-blind, randomized, dose-response, placebo-controlled study for 24 weeks. It included 12 white, male, pediatric patients (age range 7-13, mean 9.4 years) with a mean 6-minute walking distance at baseline of 363 meters (substantially decreased from the mean distance of 500-700 meters expected in healthy children).[11] Patients were randomized (1:1:1) to eteplirsen 50 mg/kg weekly, eteplirsen 30 mg/kg weekly, or placebo.[11] After 24 weeks, patients were enrolled in a long-term open-label extension study (Study 2). In this study, patients initially randomized to the placebo group were re-randomized to eteplirsen 30 or 50 mg/kg/week for which data is available up to 240 weeks (4.6 years).[1] The primary outcomes for these studies included the level of dystrophin protein in muscle tissue (measured as a percentage of the expected normal levels in healthy patients without DMD) and change in the 6MWT.[11] Study 3 is an ongoing, unpublished, interim analysis of an open-label study which evaluated the change in dystrophin levels for 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks.[1]

No difference was observed in the 6MWT at 24 weeks compared to placebo.[11] In addition, the long-term extension study failed to demonstrate a statistically significant difference in 6MWT upon comparison to placebo at 48 weeks.[1] Since all patients were re-randomized to treatment, the manufacturer attempted to compare eteplirsen to a control group generated from two DMD natural history cohorts of patients in an open-label extension of the primary study. Patients were matched to 13 historical controls based on corticosteroid use, available longitudinal data for the 6MWT, age (less than or greater than 7 years), and genotype.[1,2] Patients were not matched on the basis of the 6MWT distance though mean distance was similar between groups at baseline (363 vs. 358 meters).[2] Overall, compared to the historical control, patients treated with eteplirsen experienced a benefit of 162 meters at 36 months (3 years) in the 6MWT ($p=0.0005$).[1] The manufacturer also claimed that only 2 patients (16.7%) treated with eteplirsen lost ambulation over 4 years compared to 76.9% (10/13) of untreated historical controls.[1] However, when results are evaluated as a function of age, 6 patients (4 less than 14 years of age and 2 still ambulatory between 13 and 14 years of age) appear to have similar disease progression and functional decline compared to their age-matched, untreated historical controls.[1] All patients treated with eteplirsen had progressive decline in other functional outcomes including NSAA scores with no apparent difference from the untreated historical control.[1]

There are significant concerns and inherent limitations of using a historical control group and conclusions cannot be made from this fatally flawed study. Performance on the 6MWT is susceptible to expectation bias and coaching which significantly confounds the benefit observed in an open-label trial when compared to a historical cohort. For example, in patients treated with eteplirsen, the maximum distance achieved in the 6MWT was recorded, whereas the standard approach for historical controls was to classify patients as non-ambulatory if they were unable to complete the 6MWT.[1] If a standard assessment for the 6MWT was applied to both groups, several patients treated with eteplirsen may have been classified as non-ambulatory. It is also unclear whether physical therapy programs were similar between the treatment group and historical control.[1,2] In addition, there were significant differences between groups in steroid

regimens used and the mean age at initiation of steroid treatment (6.4 years in historical control vs. 5.2 years in treatment group).[1] These differences affect interpretation and bias results in favor of eteplirsen treatment. Historical control patients also had a lower mean NSAA scores at baseline, indicating greater disease severity and could bias results in favor of eteplirsen treatment.[1] The historical control population was selected after publication of results in eteplirsen trials and was not specified *a priori.* There is a high risk of selection, performance, detection, and reporting bias in this study and efficacy results should not be considered in the decision-making process.

The additional outcome in Study 1 and 2 was mean change in percent of dystrophin-positive fibers from baseline.[1] Biopsies through week 48 were collected from the biceps and week 180 biopsies were collected from the deltoid.[1] Because different muscle groups are known to have varying levels of dystrophin protein, comparisons of the deltoid biopsy at week 180 to earlier samples taken from the biceps are difficult to interpret. Evaluation of a different muscle group may result in varying levels of dystrophin protein. Dystrophin level was assessed using both immunofluorescence and Western blot techniques. These provide very different insight into perceived benefit of eteplirsen. Western blot is a quantitative method whereas immunofluorescence is used to identify localization of a protein in a particular tissue and is considered to be less quantitative.[1] Due to significant methodological and technical issues with the initial analyses, the FDA concluded that the results were unreliable and uninterpretable.[12] The FDA required a blinded re-analysis of available biopsies by 3 independent evaluators.[1]

After 3.5 years of treatment, patients treated with eteplirsen (both 30 and 50 mg/kg/week) had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Approximately one-third of patients had no change in dystrophin level or changes that were below the level of quantification (0.24% of normal).[1] Only one patient had a dystrophin level greater than 2% and none had a level greater than 3% of normal.[1] Overall, re-analyzed biopsies did not confirm the initial study findings and did not support the dose dependent effect seen in earlier trials. In addition, there was a poor correlation between results of immunofluorescence and Western blot analyses, and results of the immunofluorescent tests varied between treatment groups.

Despite re-analysis of biopsy samples, there are several significant limitations which should be taken into consideration. Only 3 patients had baseline samples that were evaluable upon re-analysis, and therefore, the change in dystrophin level from baseline could not be assessed.[1] Furthermore, immunofluorescent samples at 48 weeks (11 months) and Western blot analysis at 180 weeks (3.5 years) were processed differently and were not comparable with earlier samples.[1] There was also significant intra-patient variability upon Western blot analysis at 180 weeks. At least 3 patients had analyses which differed by more than 0.7% of normal between samples evaluated at 180 weeks.[1] Furthermore, the methods used to select the group of historical controls is unclear, and they may not represent a random sample of comparative patients, decreasing confidence in the results which indicate protein level was only 0.93% of normal.[1] In addition, biopsy samples were stored for approximately 3 years before re-analyzed and the stability of the protein over time was not evaluated.[1]

Study 3 is an ongoing, unpublished, open-label study including 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks (mean age of 8.9 years).[1] Data was available from 12 of these patients.[1] The primary outcome evaluated change in dystrophin protein level (evaluated using Western blot analysis). No functional outcomes were evaluated in this study. Protein levels that were below the level of quantification (0.24%) were analyzed using several imputation methods including minimum (0%), maximum (0.24%), and actual measured values. Results were consistent between all analyses, and demonstrated statistically significant differences in dystrophin level compared to baseline.[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] At 48 weeks, approximately 60% of patients treated in this study had no change in dystrophin level or had a change less than 0.25% compared to the normal level in a health patient. Only one patient had a dystrophin level greater than 1% and none had a level greater than 2% of normal.[1] These changes in dystrophin levels are not clinically significant and do not translate into any clinical meaningful benefit.

Efficacy of eteplirsen for DMD remains to be established. Data from Western blot analysis suggests that some patients may not respond to treatment with little to no improvement in dystrophin levels.[1] The FDA recommended further post-marketing studies to evaluate efficacy at higher doses.[1] Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes did not correlate with any clinical improvement. It remains to be determined if changes in dystrophin correlate to clinical outcomes, and the FDA has required further studies to evaluate functional improvements in patients with DMD.[3] FDA approval of eteplirsen was highly controversial because it conflicted with the recommendation by the external advisory committee who expressed multiple concerns with the studies, including: industry funding, blinding procedures, assays used, small sample size, and very minimal change from baseline.

Clinical Safety:

The safety population included a total of 114 patients treated with at least 1 dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Because the population is small and the majority of these trials were not placebo-controlled, there is limited data available regarding adverse effects and safety. Serious adverse events occurred in 6 patients (5.3%) and included wound infection, vomiting, fractures, decreased oxygen saturation, and viral lymphadenitis.[1] All events were thought to be unrelated to treatment. One patient, who had preexisting cardiomyopathy, experienced a decreased left ventricular ejection and discontinued treatment.[1] In general, serious and severe adverse effects were consistent with expected events for a population of patients with DMD. However, there is insufficient data to assess short-term or long-term safety of eteplirsen.

Table 1. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Eteplirsen binds to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Skipping of exon 51 allows for formation of a truncated dystrophin protein.
Distribution and Protein Binding	Protein binding: 6-17% Volume of distribution at steady state: 600 mL/kg
Elimination	Approximately 67% of eteplirsen is renally cleared Majority of drug elimination occurred within 24 hours
Half-Life	3-4 hours
Metabolism	No hepatic metabolism apparent

Abbreviations:

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Functional or symptom improvement
2) Quality of life
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Mean change in the percentage of dystrophin-positive fibers
2) Change in the 6-minute walk test at 48 weeks

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mendell, et al. 2013.[11] Exondys 51 FDA Medical Review.[1] Exondys 51 FDA Summary Review.[12] DB, PC, Phase IIB RCT	1. Eteplirsen 30 mg/kg/ week 2. Eteplirsen 50 mg/kg/ week 3. Placebo/ delayed tx After 24 weeks patients in the placebo group were randomized to one of the treatment groups in an open label extension study up to 48 weeks. Patients have been continued in the extension study for greater than 4 years.	Demographics: - Mean age: 9.4 years - Deflazacort 18-25 mg/day: 8/12 (67%) - Prednisone: 4/12 (33%) - Mean 6MWT: 363 m (range 261-456) Key Inclusion Criteria: - Boys age 7 to 13 - Confirmed DMD deletions potentially correctable by exon 51 skipping - 6MWT of 200-400 m - On stable glucocorticoid tx for ≥24 weeks - Stable cardiac and pulmonary function Key Exclusion Criteria: - None	ITT: 1. 4 2. 4 3. 4 mITT: 1. 2 2. 4 3. 4 Attrition: All patients completed 48 weeks	Primary Endpoints (ITT):[1] Mean change in percent of dystrophin-positive fibers from baseline to 12 or 24 weeks[T]** 1. 13% 2. 2% 3. -1% P-values NR Mean change in percent of dystrophin-positive fibers from baseline to 48 weeks** 1. 9% 2. 10% 3. -1% P-values NR Mean percent of normal dystrophin at 180 weeks (SD) with Western blot analysis[12] 1. 0.96% (0.95) 2. 0.91% (0.79) Mean change in 6MWT at 48 weeks (SE) 1. -153.4 m (38.7) 2. 21 m (38.2) 3. -68.4 m (37.6) p-values NR Secondary Endpoints (ITT): Mean change in 6MWT at 24 weeks (SE) 1. -128.2 m (31.6) 2. -0.3 m (31.2) 3. -25.8 m (30.6) p-values NR	NA NA NA NA	No serious or treatment -emergent adverse effects reported at 48 weeks.	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization methods and allocation concealment were unclear. Average baseline 6MWT in patients randomized to 30 mg/kg/week was ~40 m less than other groups. Performance Bias: UNCLEAR. Methods of blinding were not stated. Placebo consisted of phosphate buffered saline. Placebo or eteplirsen was diluted in normal saline and infused over 60 minutes. Detection Bias: HIGH. Biopsy samples were not processed consistently at all time points leading to unclear changes over time. Use of immunofluorescent staining was less quantitative than Western blot analysis. Re-analysis by blinded, independent pathologists (reported here) resulted in significantly differing protein levels. Analysis confirmed by Western blot at 180 weeks. Multiple methodological limitations reduce confidence in the results and limit ability to make conclusions regarding dystrophin level. Attrition Bias: HIGH. All patients remained in the study up to 48 weeks. Use of ITT appropriate. The mITT population excludes 2 patients who had rapid disease progression and became non-ambulatory despite treatment and increases in dystrophin-positive fibers. Reporting Bias: HIGH. Funding provided by Sarepta Therapeutics who was involved in data interpretation and editing the manuscript. Results of multiple post-hoc analyses emphasized. Results of immunofluorescent assays may be misleading as they describe the percent of fibers stained with an intensity ***above the background of the image*** and DO NOT correspond to a percent of normal levels expected in a healthy patient. **Applicability**: Patient: Small population limits ability to make conclusions. Patients were on stable dose of corticosteroid and ambulatory at baseline. Intervention: Effective dose not established. Comparator: Placebo appropriate to determine efficacy. No dose-response observed. Use of an open-label, non-controlled extension study after 24 weeks limits ability to make long-term efficacy or safety conclusions. Outcomes: Dystrophin measured using immunofluorescence, confirmed by Western blot. As reported, outcomes do not correspond to percent of normal levels expected in a healthy patient and may be misleading. Due to significant methodological issues, the change from baseline could not be determined. Correlation of 6MWT or other functional outcomes with dystrophin levels is unclear. Setting: Initial 24 weeks conducted at Nationwide Children's Hospital, open-label extension study conducted at 10 sites throughout the United States.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; ITT = intention to treat; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol, RCT = randomized controlled trial; SE = standard error; tx = treatment

Percentages were evaluated with immunofluorescent assays and represent the percent of fibers stained with an intensity ***above the background* of the image and DO NOT correspond to a percent of normal levels expected in a healthy patient.

[†]Data for 30mg/kg/week group collected at 24 weeks, 50mg/kg/week collected at 12 weeks, and placebo collected at both times.

References:

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10. Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. *Neuromuscul Disord.* 2010;20(11):712-716.
11. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol.* 2013;74(5):637-647.
12. Exondys 51 Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf. Accessed February 2, 2017.

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 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 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:
- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800FDA-1088 or *www.fda.gov/medwatch*.
Revised: 09/2016

Drugs for Duchenne Muscular Dystrophy

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

Length of Authorization:
- 6 months

Requires PA:
- Eteplirsen
- Deflazacort

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Eteplirsen and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for continuation of eteplirsen treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
4. Is the patient ≥ 5 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort or other corticosteroids?	**Yes:** Approve for up to 6 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of another oral corticosteroid.
7. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: • Deletion of exons 45 to 50 • Deletion of exons 48 to 50 • Deletion of exons 49 and 50 • Deletion of exon 50 OR • Deletion of exon 52?	**Yes:** Go to #8 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
8. Has the patient been on a stable dose of corticosteroid for at least 6 months?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient ambulatory with a 6-minute walk distance greater than 200 meters?	**Yes:** Document baseline 6-minute walk distance and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Does the patient remain ambulatory?	**Yes:** Go to #2	**No:** Pass to RPh, Deny; medical appropriateness.

Renewal Criteria		
2. Has the patient maintained baseline functional level as evaluated by the following criteria: • 6-minute walking distance greater than baseline OR • 6-minute walking distance which has not declined by more than 30 meters or 10% of baseline, whichever is less?	**Yes:** Approve for up to 6 months Document functional status.	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *07/17 (SS)*
Implementation: *TBD*

Drug Use Research & Management Program
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Drug Class Literature Scan: Pancreatic Enzymes

Date of Review: July 2017

Date of Last Review: March 2014
Literature Search: 03/01/14 – 05/12/17

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

Conclusions:
- This class scan identified 1 systematic review from the Cochrane Collaboration, 1 new randomized controlled trial, 1 guideline update, and 1 new FDA safety alert.
- There is insufficient comparative evidence between pancreatic enzyme preparations. There is insufficient evidence to support a difference in safety or efficacy of pancreatic enzyme preparations among cystic fibrosis patients or subgroups.

Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Previous Conclusions:
- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects. Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzyme replacement products (PEPs) in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change in CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which can potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Other side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.

Previous Recommendations:
- Due to no apparent differences in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration concerns.

Author: D. Engen

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
Cochrane: Pancreatic Enzyme Replacement Therapy for People with Cystic Fibrosis
A 2016 Cochrane systematic review evaluated the efficacy and safety of various formulations of pancreatic enzyme replacement therapies (PERT) for cystic fibrosis patients.[1] Thirteen studies included children and adults of different age groups (n=512).[1] Eight of the trials involved children ages 1-17 years, four trials studied adults ages 21-24 years, and one study included ages 12 and older.[1] All studies were of 4 weeks duration. Seven studies compared enteric coated microspheres (ECM) with other enteric-coated preparations, four compared ECM versus another ECM, and two compared various doses of PERT.[1] Primary outcomes assessed were changes in weight, height, and body mass index (BMI).[1] Study quality was mixed as all 13 trials lacked details of randomization and allocation concealment methods, 6 of the 13 studies gave no details of blinding methods, and several studies had a high risk of attrition and reporting bias due to incomplete outcome data and selective reporting.[1] Due to heterogeneous trial data, small sample sizes, and unclear to high risk of bias in a majority of the trials, the evidence was insufficient to quantify treatment effect size of the different pancreatic enzyme formulations on the nutritional status of cystic fibrosis patients.[1]

New Guidelines:
Cystic Fibrosis Foundation
The Cystic Fibrosis Foundation published a clinical practice guideline to address nutritional care of preschool children ages 2 to 5 years old with cystic fibrosis (CF).[2] The guideline committee consisted of 16 CF pediatric experts and parents; however, non-specialists or experts in methodology were not included on the guideline committee. Overall, there are very little data in children ages 2 to 5 years old and therefore the recommendations included in the guideline are based on expert opinion and are likely to change based on additional research. Consensus recommendations included in the guideline were based on extrapolation from other CF Foundation or general pediatrics guidelines due to the small pool of subjects and gaps in evidence. An 80% agreement threshold was decided a priori for recommendations. The consensus recommendations for children of preschool-aged children with CF and pancreatic insufficiency suggests PERT be adjusted to a dose of no greater than 2500 lipase units per kilogram per meal with a maximum daily dose of 10,000 lipase units per kilogram. These recommendations are clearly consensus statements and are not systematically developed from a thorough evidence review and evaluation.

New Formulations:
No new formulations were identified.

New FDA Safety Alerts:
Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP)
The FDA updated questions and answers directed to healthcare professionals and the public about the safe use of approved PEPs.[3] The original text was posted on April 12, 2010 with the most recent version dated October 20, 2016.[3] Each question addressed a particular area of product concern. The post included information on the most current PEP products available and their FDA-approved uses, as well as important details regarding safe administration, availability, and key points for patients and prescribers.[3] Key points included:

1. Creon, Zenpep, Pancreaze, Viokace, and Pertzye are currently the only FDA-approved PEPs that are marketed in the United States.
2. PEPs are not interchangeable at the pharmacy. Patients currently taking an unapproved PEP will require a new prescription for Creon, Zenpep, Pancreaze, Viokace, or Pertzye.
3. When switching a patient to another PEP, consider starting with a similar amount of lipase enzyme, then adjust the dose based on the patient's response.
4. Recognize that the labeled contents of FDA-approved PEPs reflect the actual enzyme content of the product, whereas the labeled contents of unapproved PEPs underestimate the actual lipase content.
5. Recognize that it may take 1-2 weeks for a patient to adjust their dose of the new PEP. Individual patient response should be monitored when switching from an unapproved PEP to an approved one.

References:

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Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL
CAPSULE DR	CREON	LIPASE/PROTEASE/AMYLASE	Y
CAPSULE DR	PANCREAZE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	PERTZYE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 12	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 18	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 20	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 6	LIPASE/PROTEASE/AMYLASE	N
TABLET	VIOKACE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ZENPEP	LIPASE/PROTEASE/AMYLASE	N

Appendix 2: New Comparative Clinical Trials

A total of 9 citations were manually reviewed from the initial literature search. After further review, 8 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 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Taylor et al.[4] 2015 RCT, DB, Crossover, Noninferiority study, Multicenter	Group A: Zenpep® followed by Creon® Group B: Creon® followed by Zenpep®; 28 days per treatment arm Dosing: patients began assigned treatment at a dose as close as possible to their established PEP treatment (maximum of 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day, not to exceed a dose of 10,000 lipase units/kg of body weight per day)	One clinical feature of CF and 2 disease causing mutations in genotype or sweat chloride concentration >60 mmol/L	CFA over 72 hours calculated from dietary fat intake and stools collected during the last 3 days (72 consecutive hours) of each treatment period	No difference: Noninferiority established; LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; p = 0.297

Abbreviations: RCT = randomized clinical trial; DB = double blind; CF = cystic fibrosis; CFA = Coefficient of Fat Absorption; MD = mean difference; LS = least squares; SE = standard error

Appendix 3: Abstracts of Comparative Clinical Trials

Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15(5):675-680. doi:10.1016/j.jcf.2016.02.010.

Background:
Zenpep (APT-1008) is a pancreatic enzyme product for the treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF).

Methods:
Zenpep and Creon, both containing 25,000 lipase units, were compared in a randomized, double-blind, crossover, non-inferiority study for CF-associated EPI in patients aged ≥ 12 years. Patients on a standardized diet and stabilized treatment were randomized to two treatment sequences: Zenpep/Creon or Creon/Zenpep. The primary efficacy endpoint was the coefficient of fat absorption over 72 h (CFA-72 h).

Results:
96 patients (mean age 19.2 years, 60.4% males) were randomised with 83 completers of both sequences comprising the efficacy population. Zenpep demonstrated non-inferiority and equivalence to Creon in fat absorption (LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; p = 0.297). Safety and tolerability were similar.

Conclusions:
Zenpep is comparable with Creon in efficacy and safety for the treatment of adolescents and adults with CF-associated EPI. (NCT01641393)

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 2 2017
1 Viokase.mp.4
2 Pertzye.mp. 2
3 Pancreaze.mp. 5
4 Zenpep.mp. 9
5 Creon.mp. 59
6 Ultresa.mp. 2
7 Pancrelipase/ or pancrealipase.mp. 207
8 lipase.mp. or Lipase/ 21068
9 protease.mp. 83937
10 amylase.mp. 11735
11 8 and 9 and 10 220
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 11 450
13 limit 12 to (humans and english and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews) and last 3 years) 9

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Drug Class Literature Scan: Topical Steroids

Date of Review: July 2017

Date of Last Review: March 2015
Literature Search: 3/1/2015– 6/9/2017

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

Conclusions:
- Since the last review additional evidence has become available with the publication of 2 systematic reviews and 1 CADTH Rapid Response Report. There are also 2 new topical steroid formulations.
- There is no new comparative evidence since the last review to support a difference in safety or efficacy among equipotent topical corticosteroids.
- There is insufficient evidence that the betamethasone valerate foam formulation provides any clinical benefit over other formulations currently available.

Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Previous Conclusions:
- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- At least one agent in each of the potency categories should be preferred.

Previous Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
A 2016 Cochrane Collaboration systematic review evaluated topical treatments for scalp psoriasis.[1] Comparisons in safety and efficacy were made between very high, high, and medium-potency topical steroids, vitamin D3 analogues, corticosteroid plus vitamin D combination products, corticosteroid plus salicylic acid combination products, tar-based preparations, anthralin, salicylic acid monotherapy, and ciclopirox olamine, and calcineurin inhibitors. Fifty-nine randomized controlled trials in 11,561 participants were included. Data on age of participants were available in 38 of the studies (n=9051) with a mean age of 45.2 years. Follow-up lasted for a median duration of 2.4 weeks (range: 1-8 weeks). Primary outcomes included either lesion clearance or clinical response as measured by the 5-point Investigator's Global Assessment (IGA) scale, quality of life improvements, and adverse events leading to treatment withdrawal. The IGA scale ranges from 0 or 1 (clear) to 5 (severe disease). Investigators used the proportion of patients with at least a 2 point IGA point reduction from baseline to define clearance or clinical response to therapy in clinical trials.

Between topical steroid preparations, there was no difference found in lesion clearance or clinical response between the very high potency steroid clobetasol propionate and high potency steroid comparator betamethasone dipropionate.[1] Likewise, high potency steroids betamethasone and fluocinolone acetonide 0.025% were unable to demonstrate a significant difference in lesion clearance or response when compared to treatment with medium potency hydrocortisone 17-butyrate 0.1%.[1] Among high potency steroids, one study (n=203) of moderate quality demonstrated a higher proportion of participants achieved scalp lesion clearance with mometasone furoate than betamethasone valerate 0.1% (RR 1.84; 95% Confidence Interval (CI) 1.09 to 3.11; ARR = 14%; Number Needed to Treat (NNT) = 8), as measured by a 2-point IGA reduction. However, there was insufficient information on allocation concealment, participant and personnel blinding, and outcome assessment blinding which resulted in a unclear to high risk of bias.[1] Data from 4 studies (n=2180) demonstrated that topical steroids improved psoriatic lesion clearance in 29% of patients compared to 16% of patients on calcitriol (Relative Risk (RR) 1.82; 95% CI 1.52 to 2.18; Absolute Risk Reduction (ARR) = 13%; NNT = 8).[1] Three of the 4 studies had unclear blinding of the outcome assessment and all four studies had unclear allocation concealment which resulted in the quality of evidence downgraded to moderate risk of bias by the authors.[1] Combinations of topical steroids plus vitamin D was more effective than vitamin D alone (RR 2.28; 95% CI 1.87 to 2.78; ARR = 19%, NNT = 6; high quality evidence).[1] In three studies (n=1827), overall treatment response favored corticosteroids over vitamin D (RR 2.09; 95% CI 1.80 to 2.41; ARR = 28%, NNT=4; high quality evidence).[1] Treatment of scalp psoriasis with vitamin D appeared to increase study withdrawals due to adverse events when compared with corticosteroids (5% vs. 1%, respectively; four studies, n=2291; ARI = 4%, NNH = 25) although no study reported the nature of the adverse event requiring withdrawal.[1] There was insufficient evidence to assess efficacy and safety of additional topical agents such as salicylic acid, tar, or anthralin-based treatments.

A 2015 Cochrane Collaboration systematic review update compared the effects of topical corticosteroids on pregnancy outcomes in pregnant women.[2] Fourteen observational studies (n=1,601,515) were included in the review of multiple steroid agents with variable potency.[1] Primary outcomes assessed included congenital abnormalities, orofacial clefts, preterm delivery, or low birth weight. The majority of studies failed to find topical steroid use associated with significant increased risk of adverse pregnancy outcomes regardless of potency. Although 3 cohort studies showed an increased risk of low birth weight in women exposed to potent or very potent topical steroids, pooled data from 47,651 patients found no associated risk [RR 1.58, 95% CI 0.96 to 2.58].[2] Based on

variations within the 4 cohort studies and due to 1 study without reports of potent or very potent steroid use, the overall quality of evidence was graded by the authors as low to very low.[2]

A 2015 CADTH Rapid Response Report reviewed the clinical effectiveness of betamethasone valerate (BMV) 0.12% foam compared to BMV topical 0.1% lotion and calcipotriol for scalp psoriasis treatment.[3] The reviewers identified two studies which met inclusion criteria. The clinical measures used to assess primary outcomes were the psoriasis physical signs Sum score and the Investigator's/Physician's Global Assessment (PGA) score. The Sum score assigns a numeric value for physical characteristics of psoriasis as measured by erythema (0-4), scaling (0-4), and induration (0-4) and the total value correlates moderately well with disease severity.[4] The Investigator's/Physician's Global Assessment (IGA/PGA) Score is a reliable assessment tool which commonly exists as a 5, 6, or 7-point ordinal scale which ranges from a lower score of "clear" to a higher score indicative of "very severe psoriasis." In one study (n=241), the Sum score at 28 days was significantly lower for BMV 0.12% foam than of standard treatment, which included BMV 0.1% lotion and calcipotriol (Mean Sum Score BMV foam: 1.5 [95% CI: 1.3 – 1.7] vs. Standard treatment: 3.1 [95% CI: 2.8 – 3.4]) from a baseline value of 7.6 (95% CI: 7.3 – 7.9).[3] The same study demonstrated that BMV foam treatment resulted in a greater proportion of participants with cleared or almost cleared scalp psoriasis compared to standard treatment of corticosteroids plus calcipotriol (88% vs. 66%, p<0.001) as measured by IGA score reductions.[3] A different study demonstrated that a greater proportion of patients were completely or almost completely cleared of disease at 28 days with BMV 0.12% foam compared to BMV lotion or placebo lotion (72 % vs. 47% vs. 21% respectively, p<0.05) as measured by reductions in a 7-point IGA score[3,4] No significant differences were observed in pruritus scores between BMV foam and BMV lotion.

Guidelines:
No new guidelines identified.

New Formulations:
Ultravate® (halobetasol propionate lotion 0.05%) was FDA approved in November 2015 for the topical treatment of moderate plaque psoriasis in patients 18 years of age and older.[5] Approval was based on two identical unpublished, randomized, double-blind, vehicle-controlled studies (n=443) with moderate to severe plaque psoriasis involving 2-12% of body surface area (BSA).[6] Treatment success was defined by the proportion of patients cleared or almost cleared of scaling, erythema and plaque elevation at 2 weeks as determined by a 2-point reduction from baseline in the 5-point Investigator Global Assessment (IGA) score.[6] Overall treatment success for the first trial was 49/110 (44.5%) versus 7/111 (6.3%) (p<0.001, NNT=3) with the second trial showing similar success (49/110 [44.5%] vs. 8/112 [7.1%], p<0.001, NNT=3).[6] The most common adverse reactions were telangiectasia (1.1%) and skin atrophy (1.5%).[6]

In January, 2016 the FDA approved a 0.05% topical spray formulation of betamethasone dipropionate (Sernivo®) for the treatment of adults 18 years or older with mild to moderate plaque psoriasis.[7] Approval for the spray was based on two unpublished, multi-center, double-blind trials in subjects randomized to either Sernivo® Spray (n=352) or placebo vehicle spray (n=180) applied twice daily for 4 weeks.[7] Treatment success was defined by a two-point reduction in IGA score from a baseline of 3 (moderate) to 0 or 1 (clear or almost clear).[7] In both studies at 29 days, treatment success was achieved by a higher proportion of betamethasone diopropionate spray subjects than those on placebo (42.7% vs 11.7% and 34.5% vs 13.6%, P < .001, NNT=4 and 5, respectively).[7] Adverse reactions included pruritus (6%), burning and/or stinging (4.5%), and pain (2.3%).[7]

FDA Safety Alerts:
None identified.

References:

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5. Ultravate® (halobetasol propionate lotion 0.05%) Prescribing Information. Ranbaxy Laboratories, Inc., Jacksonville, FL 32257. Nov 2015 http://www.ultravatelotion.com/pdf/ultravatelotionpi.pdf. Accessed May 4, 2017.
6. CDER Evaluation of Ultravate® https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208183Orig1s000MedR.pdf Accessed May 4, 2017.
7. Sernivo® (betamethasone dipropionate) Prescribing Information. DPT Laboratories, Ltd., San Antonio, TX 78215. Feb 2016 http://sernivo.com/documents/sernivo-pi.pdf. Accessed April 27, 2017.

Appendix 1: Current Preferred Drug List

Generic Name	Brand Name	Form	PDL Status
ALCLOMETASONE DIPROPIONATE	ALCLOMETASONE DIPROPIONATE	CREAM (G)	Y
ALCLOMETASONE DIPROPIONATE	ALCLOMETASONE DIPROPIONATE	OINT. (G)	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	CREAM (G)	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	LOTION	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	OINT. (G)	Y
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	CREAM (G)	Y
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	OINT. (G)	Y
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	CREAM (G)	Y
CLOBETASOL PROPIONATE	TEMOVATE	CREAM (G)	Y
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	OINT. (G)	Y
CLOBETASOL PROPIONATE	TEMOVATE	OINT. (G)	Y
DESONIDE	DESONIDE	CREAM (G)	Y
DESONIDE	DESONIDE	OINT. (G)	Y
FLUOCINOLONE ACETONIDE	SYNALAR	CREAM (G)	Y
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	CREAM (G)	Y
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	SOLUTION	Y
FLUOCINOLONE ACETONIDE	SYNALAR	SOLUTION	Y
FLUOCINONIDE	FLUOCINONIDE	CREAM (G)	Y
FLUOCINONIDE	VANOS	CREAM (G)	Y
FLUOCINONIDE	FLUOCINONIDE	SOLUTION	Y
FLUOCINONIDE/EMOLLIENT BASE	FLUOCINONIDE-E	CREAM (G)	Y
HYDROCORTISONE	ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	PROCTOCORT	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-5	CREAM (G)	Y
HYDROCORTISONE	PREPARATION H	CREAM (G)	Y
HYDROCORTISONE	NOBLE FORMULA HC	CREAM (G)	Y
HYDROCORTISONE	NEOSPORIN	CREAM (G)	Y
HYDROCORTISONE	HYDROCREAM	CREAM (G)	Y
HYDROCORTISONE	ECZEMA ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-10 PLUS	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-10	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE FOR KIDS	CREAM (G)	Y
HYDROCORTISONE	CORTISONE	CREAM (G)	Y
HYDROCORTISONE	CORTAID	CREAM (G)	Y

HYDROCORTISONE	ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	HYDROCORT	CREAM (G)	Y
HYDROCORTISONE	RECORT PLUS	CREAM (G)	Y
HYDROCORTISONE	SOOTHING CARE	CREAM (G)	Y
HYDROCORTISONE	HYDROCORTISONE	CREAM (G)	Y
HYDROCORTISONE	HYDROCORTISONE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORTISONE ACETATE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORTISONE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORT	OINT. (G)	Y
HYDROCORTISONE	CORTIZONE-10	OINT. (G)	Y
HYDROCORTISONE	ANTI-ITCH	OINT. (G)	Y
HYDROCORTISONE ACETATE	HYDROCORTISONE ACETATE	CREAM (G)	Y
HYDROCORTISONE ACETATE	DERMAREST DRICORT	CREAM (G)	Y
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	SOLUTION	Y
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	CREAM (G)	Y
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	OINT. (G)	Y
TRIAMCINOLONE ACETONIDE	TRIANEX	OINT. (G)	Y
AMCINONIDE	AMCINONIDE	CREAM (G)	N
AMCINONIDE	AMCINONIDE	LOTION	N
AMCINONIDE	AMCINONIDE	OINT. (G)	N
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	GEL (GRAM)	N
BETAMETHASONE DIPROPIONATE	SERNIVO	SPRAY/PUMP	N
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	FOAM	N
BETAMETHASONE VALERATE	LUXIQ	FOAM	N
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE AF	CREAM (G)	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	CREAM (G)	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE	OINT. (G)	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	OINT. (G)	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	FOAM	N
CLOBETASOL PROPIONATE	OLUX	FOAM	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	GEL (GRAM)	N
CLOBETASOL PROPIONATE	CLOBEX	LOTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	LOTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SHAMPOO	N
CLOBETASOL PROPIONATE	CLOBEX	SHAMPOO	N
CLOBETASOL PROPIONATE	CLODAN	SHAMPOO	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SOLUTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SPRAY	N
CLOBETASOL PROPIONATE	CLOBEX	SPRAY	N
CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMOLLIENT	CREAM (G)	N
CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMULSION	FOAM	N
CLOBETASOL PROPIONATE/EMOLL	OLUX-E	FOAM	N

CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMOLLIENT	FOAM	N
CLOBETASOL/SKIN CLEANSER #28	CLODAN	KT SHM CLN	N
CLOCORTOLONE PIVALATE	CLOCORTOLONE PIVALATE	CREAM (G)	N
CLOCORTOLONE PIVALATE	CLODERM	CREAM (G)	N
DESONIDE	DESONATE	GEL (GRAM)	N
DESONIDE	DESONIDE	LOTION	N
DESOXIMETASONE	TOPICORT	CREAM (G)	N
DESOXIMETASONE	DESOXIMETASONE	CREAM (G)	N
DESOXIMETASONE	TOPICORT	GEL (GRAM)	N
DESOXIMETASONE	DESOXIMETASONE	GEL (GRAM)	N
DESOXIMETASONE	DESOXIMETASONE	OINT. (G)	N
DESOXIMETASONE	TOPICORT	OINT. (G)	N
DESOXIMETASONE	TOPICORT	SPRAY	N
DIFLORASONE DIACETATE	DIFLORASONE DIACETATE	CREAM (G)	N
DIFLORASONE DIACETATE	PSORCON	CREAM (G)	N
DIFLORASONE DIACETATE	DIFLORASONE DIACETATE	OINT. (G)	N
DIFLORASONE DIACETATE/EMOLL	APEXICON E	CREAM (G)	N
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	OIL	N
FLUOCINOLONE ACETONIDE	DERMA-SMOOTHE-FS	OIL	N
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	OINT. (G)	N
FLUOCINOLONE ACETONIDE	SYNALAR	OINT. (G)	N
FLUOCINOLONE ACETONIDE	CAPEX SHAMPOO	SHAMPOO	N
FLUOCINOLONE/EMOL CMB#65	SYNALAR	CMB ONT CR	N
FLUOCINOLONE/EMOL CMB#65	SYNALAR	CREAM (G)	N
FLUOCINOLONE/SHOWER CAP	FLUOCINOLONE ACETONIDE	OIL	N
FLUOCINOLONE/SHOWER CAP	DERMA-SMOOTHE-FS	OIL	N
FLUOCINOLONE/SKIN CLNSR28	SYNALAR TS	KIT	N
FLUOCINONIDE	FLUOCINONIDE	GEL (GRAM)	N
FLUOCINONIDE	FLUOCINONIDE	OINT. (G)	N
FLURANDRENOLIDE	FLURANDRENOLIDE	CREAM (G)	N
FLURANDRENOLIDE	FLURANDRENOLIDE	LOTION	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	CREAM (G)	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	LOTION	N
FLUTICASONE PROPIONATE	CUTIVATE	LOTION	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	OINT. (G)	N
HALCINONIDE	HALOG	CREAM (G)	N
HALCINONIDE	HALOG	OINT. (G)	N
HALOBETASOL PROPIONATE	HALOBETASOL PROPIONATE	CREAM (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	CREAM (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	LOTION	N
HALOBETASOL PROPIONATE	HALOBETASOL PROPIONATE	OINT. (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	OINT. (G)	N
HALOBETASOL/LACTIC ACID	ULTRAVATE X	CMB ONT CR	N
HALOBETASOL/LACTIC ACID	ULTRAVATE X	COMBO. PKG	N
HC/MINERAL OIL/PETROLAT,WHT	HYDROCORTISONE	OINT. (G)	N

HYDROCORTISONE	ANUSOL-HC	CREAM (G)	N
HYDROCORTISONE	HYDRO SKIN	LOTION	N
HYDROCORTISONE	HYDROCORTISONE	LOTION	N
HYDROCORTISONE	SCALPICIN	SOLUTION	N
HYDROCORTISONE	TEXACORT	SOLUTION	N
HYDROCORTISONE ACETATE	MICORT-HC	CRM/PE APP	N
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	CREAM (G)	N
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	OINT. (G)	N
HYDROCORTISONE BUTYRATE/EMOLL	HYDROCORTISONE BUTYRATE	CREAM (G)	N
HYDROCORTISONE PROBUTATE	PANDEL	CREAM (G)	N
HYDROCORTISONE VALERATE	HYDROCORTISONE VALERATE	CREAM (G)	N
HYDROCORTISONE VALERATE	HYDROCORTISONE VALERATE	OINT. (G)	N
HYDROCORTISONE/ALOE VERA	HYDROCORTISONE PLUS	CREAM (G)	N
HYDROCORTISONE/ALOE VERA	HYDROCORTISONE-ALOE	CREAM (G)	N
HYDROCORTISONE/ALOE VERA	HYDROSKIN	CREAM (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	CREAM (G)	N
MOMETASONE FUROATE	ELOCON	CREAM (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	OINT. (G)	N
MOMETASONE FUROATE	ELOCON	OINT. (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	SOLUTION	N
NEOMYCIN SULFATE/FLUOCINOLONE	NEO-SYNALAR	CREAM (G)	N
NEOMYCIN/BACITRA/POLYMYXIN/HC	CORTISPORIN	OINT. (G)	N
NEOMYCIN/FLUOCINOLONE/EMOL #65	NEO-SYNALAR	CREAM (G)	N
PREDNICARBATE	DERMATOP	CREAM (G)	N
PREDNICARBATE	PREDNICARBATE	CREAM (G)	N
PREDNICARBATE	PREDNICARBATE	OINT. (G)	N
PREDNICARBATE	DERMATOP	OINT. (G)	N
TRIAMCINOLONE ACETONIDE	KENALOG	AEROSOL	N
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	AEROSOL	N
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	LOTION	N
HYDROCORTISONE	PROCTOSOL-HC	CRM/PE APP	
HYDROCORTISONE	PROCTOZONE-HC	CRM/PE APP	
HYDROCORTISONE	PROCTO-PAK	CRM/PE APP	
HYDROCORTISONE	HYDROCORTISONE	CRM/PE APP	
HYDROCORTISONE	PROCTO-MED HC	CRM/PE APP	
HYDROCORTISONE ACETATE	MICORT-HC	CRM/PE APP	
NEOMYCIN/POLYMYXIN B SULF/HC	CORTISPORIN	CREAM (G)	

Appendix 2: New Comparative Clinical Trials

A total of 70 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2017

1 aclometasone.mp.1
2 Betamethasone Valerate/ or Betamethasone/ or betamethasone.mp.3158
3 clobetasol.mp. or Clobetasol/1019
4 Fluocinolone Acetonide/ or fluocinolone.mp.444
5 hydrocortisone.mp. or Hydrocortisone/ 29324
6 Triamcinolone Acetonide/ or Triamcinolone/ or triamcinolone.mp.5132
7 fluocortolone.mp. or Fluocortolone/55
8 diflorasone.mp. 16
9 flurandrenolide.mp. or Flurandrenolone/9
10 halobetasol.mp.28
11 prednicarbate.mp.77
12 amcinonide.mp.10
13 clocortolone.mp.8
14 desoximetasone.mp. or Desoximetasone/34
15 Fluticasone/ or fluticasone.mp.3512
16 administration, topical.mp. or Administration, Topical/21895
17 topical corticosteroid.mp.1075
18 topical corticosteroids.mp.2269

19	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 41494
20	16 or 17 or 18 23982
21	19 and 20 1931
22	limit 21 to (english language and humans and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews) and last 3 years) 70

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Drug Class Literature Scan: Antiplatelets

Date of Review: July 2017

Date of Last Review: July 2015
Literature Search: July 2015-June 2017

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

Conclusions:

- A Cochrane systematic review evaluated the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis on the outcome of graft patency.[3] The overall applicability of this systematic review to clinical practice is low and results cannot be used to make policy changes at this time. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) could not be calculated.
- There are significant new data from multiple trials, systematic reviews, and guidelines addressing the most appropriate duration of dual antiplatelet therapy (DAPT) with aspirin and other antiplatelet agent following acute coronary syndrome (ACS). Overall, the data suggests that DAPT beyond 12 months decreases ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk.
- Previous large randomized controlled trials (RCTs) have demonstrated a reduction in ischemic events with the more potent P2Y12 inhibitors (prasugrel and ticagrelor) compared to clopidogrel with an absolute risk reduction (ARR) of approximately 2%.[1,2] A recent network meta-analysis[7] and a large RCT[20] have conflicting results. The meta-analysis with many limitations found no difference in mortality, cardiovascular (CV) death, myocardial infarction (MI) or stent thrombosis with either prasugrel or ticagrelor compared to clopidogrel. Additionally, a large RCT in patients with symptomatic peripheral arterial disease found no difference in a composite CV outcome or major bleeding with ticagrelor versus clopidogrel (10.8% vs. 10.6%).
- A fixed-dose combination of aspirin and omeprazole (Yosprala®) was FDA approved in September 2016 for those patients at high risk of developing aspirin associated gastric ulcers. Approval studies demonstrated a significant reduction at 6 months in the incidence of gastric or duodenal ulcer formation compared to aspirin alone (ARR 3.8%-4.9%).[6] However, these studies remain unpublished and cannot be assessed for quality. Additionally, only patients with a history of gastric or duodenal ulcer were included in trials and comparison to aspirin alone in these high risk patients is not a clinically relevant comparison.

Recommendations:

- No changes to the PDL recommended at this time
- Review comparative costs in executive session

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Previous Conclusions:

- There is moderate quality evidence that prasugrel is associated with a lower rate of major adverse cardiovascular events (MACEs) compared to clopidogrel in patients with coronary artery disease (CAD) (OR 0.86; 95% CI 0.78 to 0.94), but also a high risk of major bleeding (OR 1.33; 95% CI 1.09 to 1.61). However, a recent meta-analysis demonstrated that the risk of MACEs far outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009).
- There is low quality evidence that short-term DAPT (less than 12 months) compared to-12 month therapy is associated with a similar rate of stent thrombosis and MI, with a reduced risk of major bleeding, while extended therapy (>12 months) compared with 12-month therapy is associated with reduction in stent thrombosis (NNT 100-250) and MI (NNT 50-125), but increased risk of major bleeding (NNH 111-325). Studies have also demonstrated an increase in all-cause mortality with extended DAPT beyond one year (2.0% vs. 1.5%; OR 1.36; 95% CI 1.00-1.85; NNH 200), driven by non-cardiovascular events. Further studies are needed to evaluate this risk and define the optimal duration of therapy. At this time, DAPT should be recommended for a year in most patients receiving a DES with high risk patients considering longer term use (up to 30 months) and patients at high risk of bleeding considering therapy for less than 6 months.
- There is moderate quality evidence that long term use (>1 year) of ticagrelor may reduce risk of myocardial infarction (MI) (NNT 118) and stroke (NNT 303), but increase risk of major bleeding (NNH 65) in patients with prior MI (more than 1 year previously) taking aspirin, based on the PEGASUS-TIMI 54 trial.
- New recommendations from the AHA for the primary prevention of stroke do not recommend antiplatelet regimens other than aspirin (and cilostazol for patients with PAD) be used for prevention of stroke due to a lack of evidence from relevant clinical trials. Primary prevention of stroke with aspirin is recommended for high risk individuals (10-year risk >10%), for persons with chronic kidney disease, and as a reasonable treatment option for patients with heart failure who do not have Atrial Fibrillation (AF) or a previous thromboembolic event.

Previous Recommendations:

- Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).
- Make cilostazol a preferred drug on the PDL

Methods:

A DERP scan searched Ovid MEDLINE from December 2015 through January 2017 using terms for included drugs. An additional 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 from January 2017 through June 2017. 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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:

Lower Limb Atherosclerosis

A Cochrane systematic review was done to determine the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis undergoing bypass grafting.[3] A total of 16 studies (n=5683) were included in the analysis. The quality of evidence was low to moderate. Many of the treatment comparisons had few data to contribute, treatment dosages varied between studies, and the majority of studies did not describe their methods of randomization, allocation concealment or blinding of outcome assessors. The primary efficacy outcome was success of therapy, measured by graft patency. Six of the studies compared aspirin (ASA) or ASA plus dipyridamole (ASA/DIP) versus placebo or no treatment. There was improved graft patency in the ASA or ASA/DIP treatment group (OR 0.42; 95% CI 0.22 to 0.83; p=0.01). However, there was no improvement in those who received venous grafts. Additionally, studies included in the comparison were very old, and ASA doses ranged from 300mg to 325 mg given two to three times daily which is not consistent with doses used in clinical practice today. There was no difference in CV events (OR 1.27; 95% CI 0.43 to 3.80; 4 trials). The data was too scarce to combine and make definitive conclusions for all other comparisons of antiplatelet agents or other comparisons were not applicable to clinical practice standards. There was one large study (n=851) that evaluated clopidogrel and ASA versus ASA alone, and there was no difference of primary patency at 24 months (OR 0.95; 95% CI 0.69 to 1.31). There were fewer cases of total bleeding in the ASA alone group compared to ASA + clopidogrel (OR 2.65; 95% CI 1.69 to 4.15), but there was no difference in severe bleeding or fatal bleeding with few events in either group. There was no difference in all-cause mortality (OR 1.44; 95% CI 0.76 to 2.72). The overall applicability of this systematic review to practice is low and results cannot be used to make policy changes at this time. Further high-quality studies evaluating clinically meaningful outcomes are necessary. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) were not able to be calculated.

Dual Antiplatelet Therapy

Three systematic reviews were published evaluating the duration of dual antiplatelet therapy (DAPT).[7–9] One review included studies with patients after acute myocardial infarction (MI), one included trials with patients after a drug-eluting stent (DES) implantation, and the third review included all secondary prevention populations. The results are consistent with previous data and guidelines suggesting that DAPT beyond 1 year decreased ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk. Since these trials only compared duration of treatment and did not compare individual antiplatelet agents, they will not impact the current preferred drug list (PDL) or prior authorization policy and will not be explored further.

Comparison of platelet adenosine diphosphate (ADP) $P2Y_{12}$ Inhibitors

A network meta-analysis to compare clinical outcomes of patients receiving clopidogrel, prasugrel, ticagrelor and cangrelor prior to or during percutaneous coronary intervention (PCI) was performed.[7] A literature search identified RCTs comparing at least 2 of the P2Y12 inhibitors in those who had a PCI. The Cochrane Collaboration tool for assessing risk of bias was used to evaluate included trials. The meta-analysis used indirect comparisons to compare each agent to clopidogrel. A total of 15 RCTs (n=54,025) were included in the meta-analysis.[7] Of the patients included in these trials, 29.4% of patients had a STEMI, 87.2% with ACS, and 92.4% underwent PCI. Compared to clopidogrel, there was no significant difference between either prasugrel or ticagrelor in all-cause mortality, CV death, MI, stent thrombosis, stroke, or major bleeding. There was an increased risk of minor bleeding with ticagrelor compared to clopidogrel (OR 1.59; 95% CI 1.10 to 5.03). Previous literature has suggested that prasugrel and ticagrelor achieve faster and greater inhibition of platelet binding compared to clopidogrel and individual RCTs have demonstrated a reduction in ischemic events after PCI for these agents compared to placebo.[7] Results of this analysis conflict with those findings. However, there are limitations of a network meta-analysis, a loss of statistical power for direct comparison, and follow-up times which varied greatly among the studies. This systematic review was not funded.

Aspirin in Peripheral Vascular Disease:

A systematic review registered in PROSPERO International prospective register of systematic reviews evaluated aspirin in patients with peripheral vascular disease.[10] A literature search limited to RCTs through January 2017 identified 11 studies that were included (n=6560). The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary efficacy outcome was all-cause mortality, and the primary safety outcome was major bleeding. The majority of trials had an unclear risk of bias due to lack of reporting of detailed methods. Two trials had a low risk of bias. Using the GRADE assessment tool, the level of evidence was considered low to moderate. Results from 9 trials found no difference in the incidence in all-cause mortality with aspirin versus control (7.7% vs. 8.5%; RR -0.93; 95% CI 0.8 to 1.1).[10] The incidence of MI and stroke were also similar between both groups. There was no difference incidence of major bleeding with aspirin compared to control (1.3% vs. 1.1%; RR 1.59; 95% CI 0.96 to 2.62).[10] These results conflict with recent guideline recommendations for aspirin in symptomatic peripheral vascular disease. The authors point out that the guideline recommendations were made based on 3 studies only with a high risk of bias in combination with older evidence using antiplatelet agents other than aspirin.[10]

New Guidelines:

Aspirin for Primary Prevention of Cardiovascular Disease

The U.S. Preventive Services Task Force (USPSTF) updated their recommendations to prevent cardiovascular disease (CVD) in June 2016.[11] The USPSTF is an independent, voluntary body and authors had no conflicts of interest. The USPSTF commissioned 3 systematic reviews and a decision-analysis model to develop its recommendation. The following recommendations were made:

Population	Recommendation	Evidence Grade
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	the USPTF recommends initiating low-dose aspirin for the primary prevention of CVD and colorectal cancer (CRC) in those who are not at increased risk of bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin for at least 10 years	B (high certainty that the net benefit is moderate)
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate aspirin should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C (recommend selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small)
Adults younger than 50 years	Evidence is insufficient	I
Adults aged 70 years or older	Evidence is insufficient	I

Management of Patients with Lower Extremity Peripheral Artery Disease (PAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published guidelines in 2016.[12]

The guidelines were sponsored by ACC/AHA and without commercial support. Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry. Approximately half of the other members disclosed some sort of relationship with industry within 12 months prior. There was one lay volunteer/patient representative on the guideline committee; however, the majority of other members were cardiovascular specialists and the committee was missing representation from primary care or other non-specialty practitioners. A contracted methodologist and external evidence review committee addressed systematic review questions and appraised the evidence.

The following recommendations for medical therapy with antiplatelets for the patient with PAD were provided. There were no strong recommendations for one agent over another, but aspirin is the favored medication for symptomatic PAD. Clopidogrel remains an alternative.

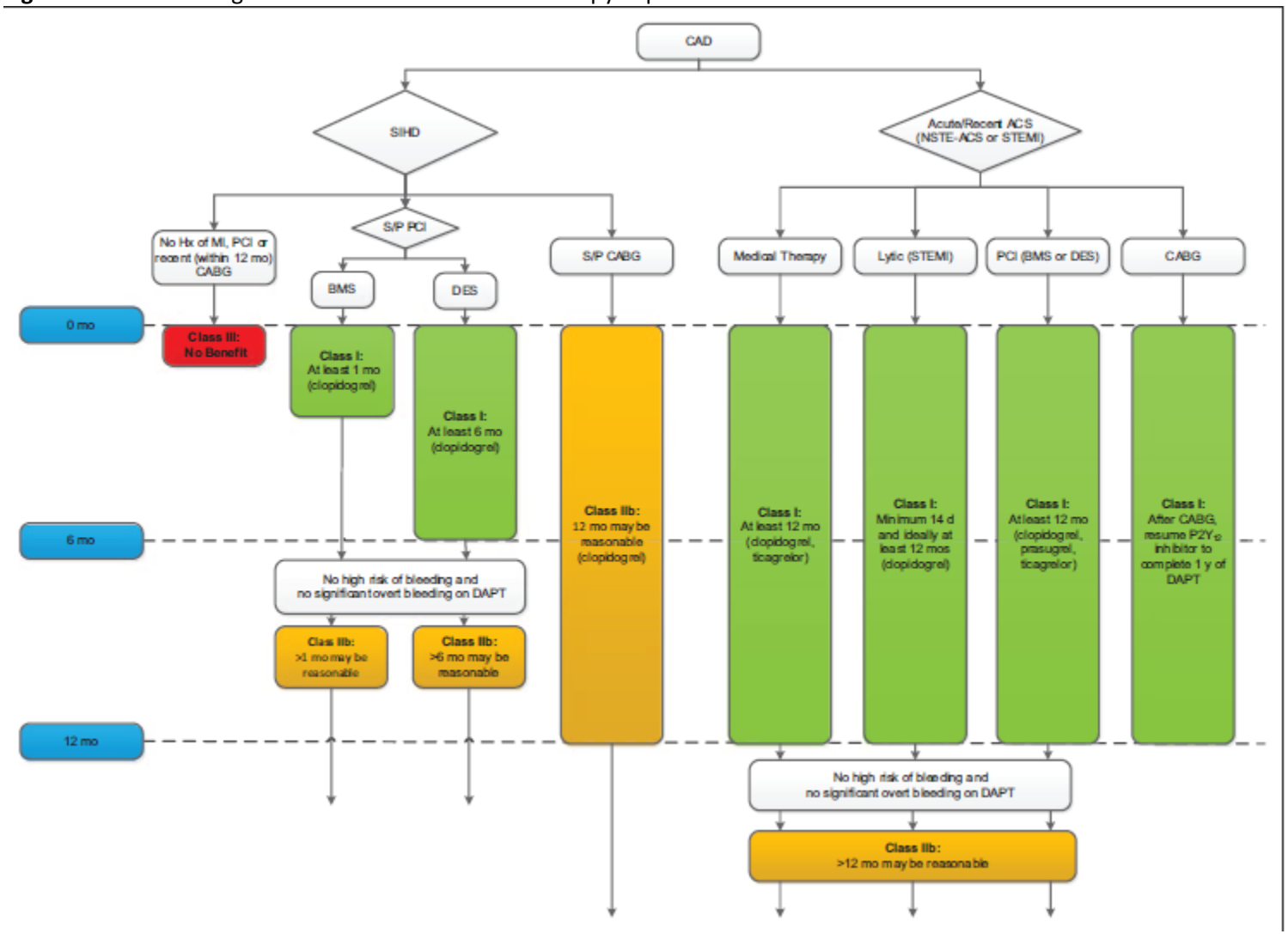
- Antiplatelet therapy with aspirin alone (75-325 mg) or clopidogrel alone is recommended to reduce myocardial infarction (MI), stroke and vascular death in patients with symptomatic PAD. Symptomatic PAD includes those with claudication and those with prior lower extremity revascularization.
    - Class of Recommendation I (Strong)
    - Level of Evidence A (high quality)
- In asymptomatic patients with PAD, antiplatelet therapy is reasonable to reduce the risk of MI, stroke or vascular death.
    - Class of Recommendation IIa (Moderate)
    - Level of Evidence C-EO (Expert Opinion)
- The effectiveness of dual antiplatelet therapy (DAPT) to reduce the risk of CV ischemic events in patients with symptomatic PAD is not well established.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)
- The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)

Duration of Dual Antiplatelet Therapy (DAPT) in Coronary Artery Disease (CAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published a focused update on DAPT in CAD in 2016.[13] This update was necessary due to 11 studies of patients with stent implantation assessing shorter-duration or longer-duration of DAPT and one large RCT assessing DAPT versus aspirin monotherapy. This guideline focused on duration of DAPT and aspirin dosing and not if one particular $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is preferred over another. Recommendations were made based on a systematic review conducted by an external evidence review committee.[14] Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry.

Overall, the new evidence supports the concept that duration of DAPT should be individualized based on risk of bleeding and ischemic risk. Longer duration compared with shorter duration of DAPT generally results in decreased ischemic risk at the expensive of an increased bleeding risk. Additionally, use of more potent $P2Y_{12}$ inhibitors in place of clopidogrel may result in decreased ischemic risk and increased bleeding risk. For patients with acute coronary syndrome (ACS), there is a strong recommendation that DAPT should be given for a minimum period of time (usually 6 to 12 months) and a weak recommendation for continuation of DAPT beyond that period of time. Additionally, shorter duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk. This is outlined in **Figure 1**.

Figure 1: Treatment algorithm for duration of DAPT therapy in patients with CAD[13]



In regards to choosing an antiplatelet, the guidelines state that "*it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel in patients with ACS treated with DAPT after coronary stent implantation and to use ticagrelor in those treated with medical therapy alone".* These are both moderate recommendations based on moderate quality evidence from 1 RCT.

New Formulations:

Yosprala® is a combination of aspirin and omeprazole approved September 2016 for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.[6] This is the only prescription fixed-dose combination of aspirin and a proton pump inhibitor and is available with both 81 and 325 mg of aspirin in combination of 40 mg of omeprazole. Approval was based on 2 unpublished, randomized, double-blind studies (n=524) over 6 months evaluating incidence of gastric ulcer formations with Yosprala compared to aspirin 325 mg alone in those at risk for developing gastric ulcers.[6] Patients had a cerebro- or cardiovascular diagnosis, were on aspirin for at least 3 months, and had a history of gastric or duodenal ulcer within the past 5 years. At month 6, the incidence of gastric or duodenal ulcer formation was lower in the Yosprala group compared to aspirin in study 1 and study 2 (3.8% vs. 8.7%; ARR 4.9%; NNT 21 and 8.5% vs. 2.7%; ARR 5.8%; NNT 18, respectively).[6] One study reported a higher rate of serious adverse events in the study group compared to aspirin alone (8.95% vs. 6.56%). Conversely, in the second study, rate of serious adverse events was higher in the aspirin group (9.06% vs. 6.06%). P-values were not reported. These studies remain unpublished and could not be assessed for quality. Results were collected from the prescribing information[6] and clinicaltrials.gov. Additionally, the comparison to aspirin alone in those with a history of an ulcer is not a clinically relevant comparison.

Long term CV and gastrointestinal (GI) safety were evaluated in a 12-month, open-label, phase 3 study in adults requiring aspirin for secondary prevention of cardiovascular or cerebrovascular events with history of a gastric or duodenal ulcer (n=380).[14] Only 290 subjects completed the 12 month study. The most common GI events were diarrhea, dyspepsia, and nausea which were reported in 4-5% of the overall population. The overall incidence of treatment emergent adverse events was 75%. Adverse events leading to study withdrawal occurred in 13.5% of subjects, with the most common reason being gastroesophageal reflux disease (1.1%).[14]

New FDA Safety Alerts:

A safety alert was released in November 2015 after an FDA review on long-term treatment with clopidogrel.[15] The FDA concluded that the long term use of clopidogrel does not increase or decrease overall risk of death in patients with heart disease and there does not appear to be an increase in the risk of cancer related deaths or cancer related adverse events.

New FDA Approved Medications:

Cangrelor (Kengreal™) is a $P2Y_{12}$ inhibitor approved on 6/22/2015 as an adjunct to PCI for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.[16] It is administered as an intravenous bolus prior to PCI followed by an infusion during the procedure. Because it is not used in outpatients, the evidence will not be evaluated further.

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CPMP 12HR	AGGRENOX	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	CPMP 12HR	ASPIRIN-DIPYRIDAMOLE ER	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	TABLET	CILOSTAZOL	CILOSTAZOL	Y
ORAL	TABLET	CLOPIDOGREL	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	PLAVIX	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	DIPYRIDAMOLE	DIPYRIDAMOLE	Y
ORAL	TAB CHEW	ASPIRIN	ASPIRIN	Y
ORAL	TAB CHEW	CHILDREN'S ASPIRIN	ASPIRIN	Y
ORAL	TABLET	ASPIRIN	ASPIRIN	Y
ORAL	TABLET DR	ASPIR 81	ASPIRIN	Y
ORAL	TABLET DR	ASPIRIN EC	ASPIRIN	Y
ORAL	TABLET DR	ASPIR-LOW	ASPIRIN	Y
ORAL	TABLET DR	ECPIRIN	ASPIRIN	Y
ORAL	TABLET DR	LOW DOSE ASPIRIN EC	ASPIRIN	Y
ORAL	CAP ER 24H	DURLAZA	ASPIRIN	N
ORAL	TABLET	BRILINTA	TICAGRELOR	N
ORAL	TABLET	EFFIENT	PRASUGREL HCL	N
ORAL	TABLET	TICLOPIDINE HCL	TICLOPIDINE HCL	N
ORAL	TABLET	ZONTIVITY	VORAPAXAR SULFATE	N

Appendix 2: New Comparative Clinical Trials

A total of 13 citations were manually reviewed from the initial literature search and an additional 5 were reviewed from the DERP scan. After further review, 15 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (platelet reactivity, platelet aggregation rates, mean platelet volume). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
PHILO[17] RCT, DB	Clopidogrel vs. ticagrelor	ACS in patients in Asia treated with PCI on background aspirin	Time to occurrence of myocardial infarction, stroke or death from vascular causes	Composite CV outcome: Clo: 25 (6.3%) Tic: 36 (9.0%) HR 1.47; 95% CI 0.88 to 2.44 Major Bleeding: Clo: 26 (6.8%) Tic: 40 (10.3%) HR 1.54; 95% CI 0.94 to 2.53
He at al.[18] RCT, open-label	Clopidogrel + ASA vs. ASA	Minor stroke or TIA	Neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days after admission	Deterioration of stroke: Clo+ASA: 9 ASA: 19 *Statistics not provided
Johnston et al.[19] RCT, DB	Ticagrelor vs. ASA	Non-severe ischemic stroke or high-risk TIA	Time to occurrence of stroke, myocardial infarction, or death within 90 days	Composite of stroke, myocardial infarction, or death Tic: 442/6589 (6.7%) ASA: 497/6610 (7.5%) HR 0.89; 95% CI 0.78 to 1.01 Major Bleeding: Tic: 31(0.5%) ASA: 38 (0.6%) HR 0.83; 95% CI 0.52 to 1.34
Hiatt et al.[20] RCT, DB	Ticagrelor vs. Clopidogrel	Symptomatic peripheral arterial disease	Composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke	Composite CV outcome: Clo: 740 (10.6%) Tic: 751 (10.8%) HR 1.02; 05% CI 0.92 to 1.13 P=NS Major Bleeding: Clo: 109 (1.6%) Tic: 113 (1.6%) HR 1.10; 95% CI

Abbreviations: ASA = aspirin; DB = double blind; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; TIA = transient ischemic attack

1. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. *Circ J*. 2015;79(11):2452-60. doi: 10.1253/circj.CJ-15-0112. Epub 2015 Sep 16.

BACKGROUND:
Few data on the relative efficacy and safety of new P2Y12inhibitors such as prasugrel and ticagrelor in Japanese, Taiwanese and South Korean patients with acute coronary syndromes (ACS) exist.

METHODS AND RESULTS:
The multicenter, double-blind, randomized PHILO trial compared the safety and efficacy of ticagrelor vs. clopidogrel in 801 patients with ACS (Japanese, n=721; Taiwanese, n=35; South Korean, n=44; unknown ethnicity, n=1). All were planned to undergo percutaneous coronary intervention and randomized within 24 h of symptom onset. Primary safety and efficacy endpoints were time to first occurrence of any major bleeding event and to any event from the composite of myocardial infarction, stroke or death from vascular causes, respectively.At 12 months, overall major bleeding occurred in 10.3% of ticagrelor-treated patients and in 6.8% of clopidogrel-treated patients (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94-2.53); the composite primary efficacy endpoint occurred in 9.0% and in 6.3% of ticagrelor- and clopidogrel-treated patients, respectively (HR, 1.47; 95% CI: 0.88-2.44). For both analyses, the difference between groups was not statistically significant.

CONCLUSIONS:
In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population.

2. He F, Xia C, Zhang JH, Li XQ, Zhou ZH, Li FP, Li W, Lv Y, Chen HS. Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. *J Clin Neurosci.* 2015 Jan;22(1):83-6. doi: 10.1016/j.jocn.2014.05.038. Epub 2014 Sep 10.

Abstract
Recent studies have suggested that combination antiplatelet therapy may be superior to monotherapy in the treatment of acute stroke. However, additional prospective studies are needed to confirm this finding. The present trial compared the efficacy and safety of clopidogrel plus aspirin versus aspirin alone in the treatment of non-cardioembolic ischemic stroke within 72 hours of onset. Six hundred and ninety patients aged $\geqslant$ 40 years with minor stroke or transient ischemic attack (TIA) were identified for enrollment. Experienced physicians determined baseline National Institutes of Health Stroke Scale scores at the time of admission. All patients were randomly allocated (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100mg/day). The main endpoints were neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days of admission. After 43 patients were excluded, 321 patients in the dual therapy group and 326 patients in the monotherapy group completed the treatment. Baseline characteristics were similar between groups. During the 2 week period, stroke deterioration occurred in nine patients in the dual therapy group and 19 patients in the monotherapy group. Stroke occurred after TIA in one patient in the dual therapy group and three patients in the monotherapy group. Similar

numbers of adverse events occurred in both groups. This study showed that early dual antiplatelet treatment reduced early neurological deterioration in patients with acute ischemic stroke, compared with antiplatelet monotherapy. These results imply that dual antiplatelet therapy is superior to monotherapy in the early treatment of acute ischemic stroke.

3. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med.* 2016 Jul 7;375(1):35-43. doi: 10.1056/NEJMoa1603060. Epub 2016 May 10.

BACKGROUND:
Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischemia.

METHODS:
We conducted an international double-blind, controlled trial in 674 centers in 33 countries, in which 13,199 patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2 through 90). The primary end point was the time to the occurrence of stroke, myocardial infarction, or death within 90 days.

RESULTS:
During the 90 days of treatment, a primary end-point event occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio, 0.87; 95% CI, 0.76 to 1.00). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.

CONCLUSIONS:
In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.).

4. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med*. 2017 Jan 5;376(1):32-40. doi: 10.1056/NEJMoa1611688. Epub 2016 Nov 13.

BACKGROUND:

Peripheral artery disease is considered to be a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. Data from previous trials have suggested that patients receiving clopidogrel monotherapy had a lower risk of cardiovascular events than those receiving aspirin. We wanted to compare clopidogrel with ticagrelor, a potent antiplatelet agent, in patients with peripheral artery disease.

METHODS:
In this double-blind, event-driven trial, we randomly assigned 13,885 patients with symptomatic peripheral artery disease to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patients were eligible if they had an ankle-brachial index (ABI) of 0.80 or less or had undergone previous revascularization of the lower limbs. The primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety end point was major bleeding. The median follow-up was 30 months.

RESULTS:
The median age of the patients was 66 years, and 72% were men; 43% were enrolled on the basis of the ABI and 57% on the basis of previous revascularization. The mean baseline ABI in all patients was 0.71, 76.6% of the patients had claudication, and 4.6% had critical limb ischemia. The primary efficacy end point occurred in 751 of 6930 patients (10.8%) receiving ticagrelor and in 740 of 6955 (10.6%) receiving clopidogrel (hazard ratio, 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65). In each group, acute limb ischemia occurred in 1.7% of the patients (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85) and major bleeding in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49).

CONCLUSIONS:
In patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups. (Funded by AstraZeneca; EUCLID ClinicalTrials.gov number, NCT01732822 .).

Appendix 4: Medline Search Strategy

1	Platelet Aggregation Inhibitors/ or antiplatelets.mp.	27809
2	aspirin.mp. or Aspirin/	33795
3	Aspirin/	22000
4	Dipyridamole/ or Aspirin, Dipyridamole Drug Combination/	2499
5	clopidogrel.mp.	10526
6	ticagrelor.mp.	1229
7	prasugrel.mp. or Prasugrel Hydrochloride/	1540
8	Ticlopidine/ or ticlodipine.mp.	8530
9	vorapaxar.mp.	191
10	acute coronary syndrome.mp. or Acute Coronary Syndrome/	17978
11	Coronary Artery Bypass/ or Myocardial Revascularization/ or Angioplasty, Balloon, Coronary/ or coronary revascularization.mp.	62248
12	Stents/ or drug eluding stent.mp.	53562
13	Arterial Occlusive Diseases/ or Cerebral Infarction/ or Stroke/ or ischemic stroke.mp. or Ischemic Attack, Transient/	107484
14	peripheral vascular disease.mp. or Peripheral Vascular Diseases/	11432
15	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9	54413
16	10 or 11 or 12 or 13 or 14	229804
17	15 and 16	15201
18	limit 17 to (english language and humans and yr="2017 -Current" and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or systematic reviews))	13

Antiplatelets

Goal:

- Approve antiplatelet drugs for funded diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is this continuation of hospital treatment?	**Yes:** Approve for 30 days only and inform provider of preferred products.	**No:** Go to #5

Approval Criteria		
5. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

FDA Approved Indications (July 2017)

	2º Stroke	2º PAD	2º MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

Abbreviations: 2º = secondary prevention; ACS=Acute Coronary Syndrome; ASA/DP ER = aspirin/dipyridamole; CI=contraindication; PCI=Percutaneous Intervention; X = FDA-approved indication.

P&T / DUR Review: *7/17; (MH) 7/15 (KK); 11/11*
Implementation: *10/15, 8/15; 7/31/14; 4/9/12*

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Drug Class Literature Scan: Topical Antipsoriatics

Date of Review: July 2017

Date of Last Review: January 2015
Literature Search: 01/01/15 – 04/30/17

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

Conclusions:
- Since the last review additional evidence has become available with the publication of 1 systematic review. One new combination vitamin D analogue/corticosteroid product has been approved by the Food and Drug Administration (FDA).
- There is insufficient comparative evidence to support differences in safety or efficacy among non-steroidal topical antipsoriatics.
- For scalp psoriasis clearance, one systematic review found that combinations of topical corticosteroids plus vitamin D are more effective than topical vitamin D monotherapy with a NNT of 6.
- For scalp psoriasis clearance, one systematic review found that topical corticosteroid monotherapy is more effective than topical vitamin D monotherapy with a NNT of 4.

Recommendations:
- No changes are recommended to the OHP PDL based on the review of current evidence. Assign coal tar preparations to antipsoriatic class as non-preferred products. Review comparative drug costs in the executive session.

Previous Conclusions:
- First line therapy for psoriasis remains traditional topical therapies, including corticosteroids, vitamin D and vitamin D analogues, dithranol (anthralin), and tar preparations.
- There is no evidence of a significant difference in efficacy/effectiveness or harms between the different vitamin D analogues.
- Combination therapy with a vitamin D analogue and corticosteroid has proved to be more effective than either component alone.
- Calcipotriene is recommended first line in childhood psoriasis.
- There is lower strength of evidence for the efficacy of anthralin and it should be used as alternative therapy after vitamin D analogues and/or corticosteroids.

Previous Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Author: D. Engen

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:

Cochrane: Topical Treatments for Scalp Psoriasis
A 2016 Cochrane Collaboration systematic review evaluated the efficacy and safety of topical treatments for scalp psoriasis.[1] Main comparators included topical steroids, vitamin D3 analogues, and corticosteroid plus vitamin D combination products. Other comparators included corticosteroid plus salicylic acid combination products, tar-based preparations, anthralin, and salicylic acid monotherapy. Fifty-nine randomized controlled trials in 11,561 participants were included. Data on age of participants were available in 38 of the studies (n=9051) with a mean age of 45.2 years.[1] Few studies included children. Follow-up lasted for a median duration of 2.4 weeks (range: 1-8 weeks).[1] Primary outcomes included either lesion clearance or clinical response as measured by the 5-point Investigator's Global Assessment (IGA) scale.[1] The 5-point IGA scale has been used in evaluation of psoriasis severity in clinical trials and correlates with other common psoriasis assessment tools but is not as well validated.[2] Additional primary outcomes assessed were quality of life improvements and adverse events leading to treatment withdrawal.

Six studies assessed combination vitamin D/steroid preparations versus vitamin D monotherapy for topical psoriatic lesion clearance.[1] Four of the 6 studies (n=2008) addressed IGA clearance as the primary outcome measure.[1] Combinations of topical steroids plus vitamin D were more effective than vitamin D alone (Relative Risk (RR) 2.28; 95% Confidence Interval (CI) 1.87 to 2.78; Absolute Risk Reduction (ARR) = 19%, Number Needed to Treat (NNT) = 6; high quality evidence).[1] However, in three studies (n=1827), overall treatment response favored corticosteroid monotherapy over vitamin D monotherapy (RR 2.09; 95% CI 1.80 to 2.41; ARR = 28%, NNT = 4; high quality evidence).[1] Meta-analysis of 4 studies (n=2291) indicated more participants withdrew due to adverse events for treatment with vitamin D monotherapy versus steroid monotherapy (5% vs. 1%, respectively; Absolute Risk Increase (ARI) = 4%, Number Needed to Harm (NNH) = 25) although no study reported on the nature of the adverse event requiring withdrawal.[1] Data from 4 studies (n=2180) demonstrated that topical steroids improved psoriatic lesion clearance in 29% of patients compared to 16% of patients on calcitriol as measured with the IGA scale (RR 1.82; 95% CI 1.52 to 2.18; ARR = 13%; NNT = 8).[1] All four studies had unclear allocation concealment and 3 of the 4 studies had unclear blinding of outcome assessments which resulted in the quality of evidence downgraded to moderate risk of bias by the authors. There was insufficient evidence to assess efficacy and safety of additional topical agents such as salicylic acid, tar- or anthralin-based treatments.[1]

New Guidelines:
None identified.

New Formulations:
In 2015, the FDA approved Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) topical foam for the treatment of plaque psoriasis in patients 18 years and older.[3] Enstilar® is applied to affected areas once daily for up to 4 weeks.[3] Approval for the foam was based on one phase 2 and one phase 3 multicenter, randomized, double-blind trial (n=728) in subjects with mild to severe psoriasis.[4] Disease severity was graded using a 5-point Investigator's Global Assessment (IGA) and at least 75% of subjects in each study were classified with "moderate" psoriasis at baseline.[4] Successful treatment outcomes were defined as the proportion of subjects at week 4 who were "Clear" to "Almost Clear" of psoriatic lesions.[4] Trial 1 (n=302) compared three treatment groups: Enstilar Foam, betamethasone dipropionate in vehicle, or calcipotriene hydrate in vehicle. The difference in proportion of subjects with successful clearance was higher for Enstilar Foam compared to calcipotriene monotherapy (45% vs. 15%, respectively; p<0.001; ARR = 30%, NNT=4) and versus betamethasone dipropionate alone (45% vs. 31%; p=0.047; ARR = 14%, NNT = 8).[4] Trial 2 (n=426) compared Enstilar Foam to vehicle. For trial 2, the proportion of subjects with treatment success was 53% for Enstilar foam versus 5% for vehicle (p<0.001; ARR = 48%, NNT = 3).[4,5] The most commonly reported adverse events for those treated with Enstilar were nasopharyngitis (2%), increased blood pressure (1%), as well as application site pain (2%), pruritus (1%), and irritation (1%).[5]

New FDA Safety Alerts:
None identified.

References:

1. Schlager JG, Rosumeck S, Werner RN, et al. Topical treatments for scalp psoriasis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD009687.pub2/abstract. Accessed April 11, 2017.
2. Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. Journal of Dermatological Treatment. 2015;26(1):23-31. doi:10.3109/09546634.2013.865009. Accessed June 16, 2017.
3. Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) Prescribing Information. LEO Pharma Inc. 1 Sylvan Way, Parsippany, NJ 07054. Oct 2015 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207589s000lbl.pdf. Accessed June 1, 2017.
4. CDER Evaluation of Enstilar® https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207589Orig1s000ClinPharmR.pdf. Accessed June 1, 2017.
5. Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and Safety of Calcipotriene Plus Betamethasone Dipropionate Aerosol Foam in Patients With Psoriasis Vulgaris--a Randomized Phase III Study (PSO-FAST). Journal of Drugs in Dermatology. 2015;14(12):1468-1477.

Appendix 1: Current Preferred Drug List

Antipsoriatic Agents

Formulation	Brand	Generic	PDL
CREAM (G)	CALCIPOTRIENE	CALCIPOTRIENE	Y
SOLUTION	CALCIPOTRIENE	CALCIPOTRIENE	Y
OINT. (G)	CALCIPOTRIENE-BETAMETHASONE DP	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	DOVONEX	CALCIPOTRIENE	Y
OINT. (G)	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	TAZAROTENE	TAZAROTENE	Y
CREAM (G)	TAZORAC	TAZAROTENE	Y
GEL (GRAM)	TAZORAC	TAZAROTENE	Y
CREAM (G)	DRITHOCREME HP	ANTHRALIN	N
CREAM (G)	ANTHRALIN	ANTHRALIN	N
SHAMPOO(G)	ZITHRANOL	ANTHRALIN MICRONIZED	N
OINT. (G)	CALCIPOTRIENE	CALCIPOTRIENE	N
OINT. (G)	CALCITRENE	CALCIPOTRIENE	N
FOAM	SORILUX	CALCIPOTRIENE	N
SUSPENSION	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	N
FOAM	ENSTILAR	CALCIPOTRIENE/BETAMETHASONE	N
OINT. (G)	CALCITRIOL	CALCITRIOL	N
OINT. (G)	VECTICAL	CALCITRIOL	N
FOAM	PSORIATAR	COAL TAR	N
FOAM	SCYTERA	COAL TAR	N
OINT. (G)	MG217 PSORIASIS	COAL TAR	N
CREAM (G)	SORBOLENE	GLYCERN/MIN OIL/PETROLAT/C.ALC	N
CREAM (G)	AVAGE	TAZAROTENE	N

Coal Tar Products

FormDesc	Brand	Generic	PDL
SHAMPOO	ANTI-DANDRUFF	COAL TAR	
SHAMPOO	BETATAR	COAL TAR	
SOLUTION	COAL TAR	COAL TAR	
EMULSION	CUTAR	COAL TAR	
SHAMPOO	DHS TAR	COAL TAR	
SHAMPOO	DHS TAR GEL	COAL TAR	

SHAMPOO	DUPLEX T	COAL TAR
SHAMPOO	IONIL T	COAL TAR
LOTION	OXIPOR VHC	COAL TAR
SHAMPOO	PC TAR	COAL TAR
SHAMPOO	PENTRAX	COAL TAR
SHAMPOO	PENTRAX GOLD	COAL TAR
SHAMPOO	POLYTAR	COAL TAR
GEL (GRAM)	PSORIASIN	COAL TAR
LOTION	TEGRIN PSORIASIS	COAL TAR
SHAMPOO	TERA-GEL TAR	COAL TAR
SHAMPOO	T-GEL	COAL TAR
SHAMPOO	THERA-GEL	COAL TAR
SHAMPOO	THERAPEUTIC SHAMPOO	COAL TAR
SHAMPOO	T-PLUS	COAL TAR
SHAMPOO	X-SEB T PLUS	COAL TAR

Appendix 2: New Comparative Clinical Trials

A total of 28 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), data collection methods (eg, unblinded), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 4 2017
1 calcipotriene.mp. 773
2 calcipotriene and betamethasone.mp. 194
3 tazarotene.mp. 479
4 Calcitriol/ or calcitriol.mp. 12630
5 anthralin.mp 327
6 coal tar 701
7 psoriasis.mp. or Psoriasis/ 23589
8 1 or 2 or 3 or 4 or 5 or 6 14104
9 7 and 8 1202
limit 9 to (yr="2015 -Current" and english and humans and (clinical study or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or systematic reviews)) 28

Topical Antipsoriasis Drugs

Goal(s):

Restrict topical antipsoriasis drugs only for funded OHP diagnoses. Moderate/Severe psoriasis treatments are funded on the OHP. Treatments for mild psoriasis (L400-404, L408-418, L448), seborrheic dermatitis (L2083,L210-219,L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) and other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985) are not funded.

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis (L2083, L210-219, L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) or other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985)?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis Psoriasis? (ICD-10 L400-404,L408-418, L448)	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as: • At least 10% body surface area involved or with functional impairment • Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No:** Approve for length of treatment; maximum 1 year.
7. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.	**If funded, or clinic provides supporting literature:** Approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/17 (DE); 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

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Drug Class Literature Scan: Newer Antiemetics

Date of Review: July 2017

Date of Last Review: January 2016
Literature Search: 03/27/17 – 04/17/17

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

Conclusions:

- A search of the evidence on antiemetics identified three systematic reviews and meta-anlayses,[1–3] four guidelines,[4–7] two new formulations and one new indication.[8–10] There was insufficient evidence on subgroup populations and analyses related specifically to Medicaid patients. The evidence contributing to this review supports current antiemetic policy or lacks the quality of evidence required to prompt change to current preferred drug list (PDL) recommendations.
- A Cochrane review was performed on antiemetic use for the prevention and treatment of chemotherapy induced nausea and vomiting in children.[2] There was insufficient evidence to pool results of comparisons. Evidence was limited and firm conclusions were not identified. In a comparison of combination treatment with 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA) and dexamethasone compared to 5-HT3 RAs alone, more patients experienced no vomiting with combination therapy. A second comparison found rates of emesis were reduced with granisetron compared to ondansetron for control of vomiting in the acute phase (pooled relative risk [RR] 2.26; 95% CI, 2.04 to 2.51; ARR not available) but nausea comparisons and delayed phase results suggest similar efficacy.[2]
- A small number of trials with few patients found ondansetron to be as effective as metoclopramide in prevention of nausea symptoms and vomiting episodes in pregnant women with nausea and vomiting or hyperemesis gravidarum (low quality evidence).[1,3]
- Guidelines recommend a neurokinin 1 receptor antagonist (NK1 RA), a 5-HT3 RA and dexamethasone for the prevention of acute and delayed nausea and vomiting in patients receiving chemotherapy.[4,6] The American Society of Clinical Oncology (ASCO) guideline update recommends the NK1 RA netupitant and palonosetron (NEPA) as an option for a three-drug regimen in patients receiving highly emetogenic chemotherapy (HEC).[4] The recommendation was based on two phase three trials but was not graded. NEPA was previously reviewed and presented to the P and T committee. Conclusions are presented below.
- Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASSC/ESMO) guidelines on anticipatory nausea and vomiting in adults and children receiving chemotherapy remain unchanged from the 2011 update due to no new evidence.[5] Optimizing management of acute and delayed phase nausea and vomiting is recommended as the most effective preventative strategy for avoiding anticipatory manifestations.
- Updated guidance from MASSC/ESMO on prevention of nausea and vomiting in patients receiving chemotherapy, radiation, multiple-day chemotherapy, or high-dose chemotherapy and patients with advanced cancer, or breakthrough nausea or vomiting were published in 2016 and support the current policy recommendations for antiemetics.[6,7]

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- A new extended-release granisetron (ERG) formulation (Sustol®) was approved by the FDA to be used in combination with other antiemetics for the prevention of acute and delayed chemotherapy induced nausea and vomiting for patients receiving moderately emetogenic chemotherapy (MEC) and anthracycline and cyclophosphamide combination chemotherapy.[8] Approval was based on one trial which demonstrated ERG to be non-inferior to palonosetron.
- An extended-release formulation of doxylamine 20 mg and pyridoxine 20 mg (Bonjesta®) was approved for nausea and vomiting in pregnant women.[9] No new evidence was available for analysis. Approval was based off data demonstrating bioequivalence between two combination tablets of doxylamine 10 mg and pyridoxine 10 mg to the fixed dose combination of doxylamine 20 mg and pyridoxine 20 mg.
- Review of 2016 fourth quarter utilization data for the antiemetic class shows PDL adherence to be 98% for the preferred agent ondansetron.

Recommendations:
- Literature evaluated in this review supports the current preferred drug list (PDL) status of therapies in the antiemetic class.
- No further review or research is needed at this time. Evaluate comparative drug costs in executive session.

Previous Conclusions:
- There is insufficient new comparative effectiveness or comparative harms evidence for any given antiemetic indication.
- One new guideline for the management of chemotherapy-induced nausea and vomiting (CINV) from the National Comprehensive Cancer Network (NCCN) has been published. Key recommendations from clinical practice guidelines include up to 3 days of an antiemetic for patients beyond length of the chemotherapy regimen or radiation.
- Low strength of evidence from one systematic review and meta-analysis demonstrated that neurokinin-1 (NK1) receptor antagonists (RA) may be effective in controlling post-operative nausea and vomiting (PONV). The majority of the evidence was for aprepitant 80 mg compared to placebo, which reduced post-operative nausea, 45.2% vs. 76.1% (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting, 3.8% vs. 21.1% (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) based on 3 randomized controlled trials (RCTs) (n=224).
- Low strength of evidence from one RCT found the fixed dose combination product NEPA (netupitant 300 mg/palonosetron 0.5 mg) (Akynzeo®) to be superior to palonosetron for complete response (i.e., no rescue treatment required and no emesis) during the delayed phase (25-120 hours) in patients who received moderate emetogenic chemotherapy (MEC), 76.9% vs. 69.5% (p=0.001), number needed to treat (NNT) of 14. Guideline revisions in 2011 changed the chemotherapy regimen used in this study from a MEC designation to high emetogenic chemotherapy (HEC), providing evidence to support NEPA use in HEC. NEPA provided superior response rates compared to palonosetron for key secondary endpoints; complete response in the acute phase (0-24 hours), complete response in the overall phase (0-120 hours), no significant nausea overall and no emesis overall. External validity of this study is limited by the study participants being primarily female (98%) with breast cancer (97%).
- There is low strength of evidence from two additional trials that support the use of NEPA for MEC and HEC regimens in the acute and delayed phases in a more diverse population with a variety of malignant diseases. NEPA + dexamethasone was found to provide a complete response in 81-91% of patients, compared to 84-92% of patient taking a control regimen of aprepitant + palonosetron + dexamethasone, receiving six cycles of chemotherapy in a safety study. Evidence for the efficacy of oral palonosetron, in the acute phase after HEC, was demonstrated in a comparative trial of oral palonosetron compared to intravenous (IV) palonosetron. Complete response rates in the acute phase were higher for oral palonosetron 0.50 mg compared to IV palonosetron 0.25 mg, 76.3% vs. 70.4%.
- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (Varubi™). Currently, only prescribing information could be found.

Previous Recommendations:

- No changes are recommended to the PDL.
- Approve antiemetic PA as amended:
    - Patients who receive chemotherapy or radiation are allowed 3 days of antiemetic therapy beyond length of treatment.
    - Require PA for doxylamine/pyridoxine to cover for pregnancy-induced n/v after a failed trial of pyridoxine.
    - Require PA for NEPA and rolapitant.

Fourth Quarter 2016 Utilization:

Fourth quarter (10/1/16 through 12/31/16) utilization data for the newer antiemetics for the Oregon Medicaid fee-for-service (FFS) population shows the preferred agent, ondansetron, resulted in the majority of utilization. Claims for non-preferred agents were for doxylamine/pyridoxine (Diclegis) and rolapitant (Varubi).

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:

Cochrane: Antiemetics for the Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Childhood

A systematic review and meta-analysis evaluated pharmacotherapies used for anticipatory, acute and delayed nausea and vomiting in children (less than 18 years) who are receiving or about to receive chemotherapy.[2] Pharmacotherapies included were: 5-HT3 RAs, benzodiazepines, cannabinoids, corticosteroids, cyclizine, dopamine blockers, and levomepromazine (not available in the US). NK1 RAs and non-pharmacological therapy were not included. Thirty-four RCTs were available for analysis, 27 investigating the treatment of acute nausea and vomiting (1719 patients). Outcomes assessed included complete control of nausea (no nausea and no rescue medication) in the acute phase (first 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours of treatment with chemotherapy) and complete control of vomiting in both the acute and delayed phase. No trials assessed anticipatory nausea or vomiting. There was limited data beyond the first 24 hours of chemotherapy. Nausea outcomes were inconsistently reported and were not assessed via a validated measurement.

Pooled analysis of trial data was not possible for many of the trials due to the quality and quantity of trials identified. The effects of dexamethasone added to 5-HT3 RAs (ondansetron and granisetron) were studied in 2 trials.[2] The combination dexamethasone/5HT3 RA group completely controlled vomiting in more patients

than 5-HT3 RAs alone (RR 2.03; 95% CI, 1.35 to 3.04) (ARR not provided). Granisetron 20 mcg/kg was compared to granisetron 40 mcg/kg for complete control of vomiting and found to have similar efficacy (pooled RR 0.93; 95% CI, 0.80 to 1.07). No differences were found between granisetron 10 mcg/kg and 40 mcg/kg in controlling acute vomiting. Data from three trials suggest that granisetron was more effective than ondansetron for acute vomiting (pooled RR 2.26; 95% CI, 2.04 to 2.51); however complete control of acute nausea (pooled RR 1.05; 95% CI, 0.94 to 1.17), delayed nausea (pooled RR 1.13; 95% CI, 0.93 to 1.38) and delayed vomiting (pooled RR 1.13; 95% CI, 0.98 to 1.29) were similar between the two treatments.[2] Evidence was insufficient to make firm conclusions. Data on cannabinoids was conflicting and results were not able to be pooled.

Cochrane: Interventions for Treating Hyperemesis Gravidarum

The efficacy and safety of treatments for hyperemesis gravidarum in patients who were pregnant up to 20 weeks' gestation were included.[1] Studies of nausea and vomiting in pregnancy were excluded. Of the newer antiemetics, only 2 trials evaluated ondansetron were included in the review. Very low evidence based on one trial of 83 women found similar efficacy between metoclopramide and ondansetron. Severity of nausea and vomiting was similar between metoclopramide and ondansetron based on a 10-point visual analog scale (MD 1.70; 95% CI, -0.15 to 3.55).[1] Metoclopramide was associated with a higher incidence of drowsiness and dry mouth. A trial evaluating duration of hospital admission found no difference between ondansetron and promethazine based on very low quality evidence.

McParlin et al – Treatment for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy

In a systematic review, evidence for treatment of nausea and vomiting and hyperemesis gravidarum were reviewed.[3] Authors declared no conflict of interest and the analysis was funded by the National Institute for Health Research Technology Assessment Program. Seventy-eight trials were identified, 67 were RCTs. The American Heart Association (AHA) evidence grade and recommendation methodology was used to grade each assessment. Strength of the recommendation ranged from level A (high quality) to level C (expert opinion) and quality of evidence from class I (strong) to class III (harm). A meta-analysis was not possible due to heterogeneity and incomplete findings. A multitude of interventions were studied; however, for this analysis only results for newer antiemetics will be presented.

Five RCTs evaluated pyridoxine/doxylamine in the treatment of nausea and vomiting in pregnancy or hyperemesis gravidarum and determined the combination to be effective in women with moderate to severe symptoms as a second-line therapy (Level A, class IIa). In three trials (n=280) comparing pyridoxine/doxylamine to placebo or ondansetron, symptom improvement was demonstrated in both groups with higher rate of improvement in the pyridoxine/doxylamine group with a mean change in Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score of 4.8 versus 3. 9 (p=0.006). The PUQE measures symptoms on a scale of 0 (no symptoms) to 15 (worst possible symptoms). A small trial (n=60) in pregnant women found pyridoxine/doxylamine demonstrated reduced risk of recurrence of symptoms when used preventatively. Symptoms occurred in 15.4% of patients treated with pyridoxine/doxylamine compared to 39.1% in the group that was treated after symptoms presented (p<0.04; ARR 23.7%; NNT 4).[3] Seven RCTs with low or unclear risk of bias evaluated 5-HT3 RAs compared to placebo or active treatment. Authors concluded that 5-HT3 RAs were effective for all severity levels of nausea and vomiting (Level A, class IIa).

New Guidelines:

ASCO – Antiemetic Focused Guideline Update

A 2015 ASCO clinical practice guideline on the use of antiemetics was published to evaluate the combination of netupitant and palonosetron (NEPA) for prevention of acute and delayed nausea and vomiting due to chemotherapy.[4] ASCO guideline process is to grade the literature and make recommendations based on the strength of the evidence; however, the grading of trials included in the analysis was not provided.

ASCO recommends that patients who receive HEC (including anthracycline and cyclophosphamide) should be offered a three-drug antiemetic regimen.[4] A combination regimen of a NK1 RA, 5-HT3 RA and dexamethasone are recommended. An additional option is the combination of oral NEPA plus dexamethasone (recommendation grade not provided). Previous recommendations found in the 2011 update were unchanged:

- The preferred 5-HT3 RA for patients receiving MEC is palonosetron in addition to a corticosteroid.
- Antiemetic therapy should be based on the chemotherapy agent that has the highest emetic risk if the patient is receiving multiple chemotherapy agents.
- Patients receiving HEC should receive dexamethasone and a 5-HT3 RA.
- 5-HT3 RA and corticosteroids should be used for pediatric patients receiving MEC or HEC.
- HEC radiotherapy should be treated with a 5-HT3 RA before each fraction and a 5-day course of dexamethasone. The same recommendations apply for MEC radiotherapy, but the 5-day course of dexamethasone is optional.
- Patients receiving combination radiation therapy and chemotherapy should receive an antiemetic based on the emetogenicity of chemotherapy unless there is more risk of emesis with radiation.

2016 MASCC and ESMO Guidelines for Nausea and Vomiting Prevention in Patients Receiving Chemotherapy and Radiotherapy and in Advanced Cancer Patients

Updated MASCC/ESMO recommendations from the 2010 guideline were published on the most effective management of nausea and vomiting in patients undergoing treatment for malignancy with advanced cancer.[6] The level of evidence and the grading of the recommendations according to ESMO were based on adaptations of the grading methodology used by the Infectious Diseases Society of America (IDSA). IDSA grades the strength of the recommendation as the following: A (good evidence), B (moderate evidence) and C (poor evidence). The quality of the evidence is also graded: I (high quality from more than one randomized trials), II (evidence from more than one body of evidence that is not randomized or from a cohort or case-controlled study) or II (expert opinion evidence). The MASCC evaluates the evidence based on the levels of Scientific Confidence. The ranges were the following: high, moderate, low, very low and no confidence. Each recommendation received an assessment according to both the ESMO and MASCC. MASCC and ESMO were solely responsible for the funding the guidelines. Thirteen authors had conflicts of interest and six had none.

Treatment recommendations for prophylaxis of acute and delayed nausea and vomiting are presented in **Table 1**.[6] **Table 2** outlines the antiemetic treatment options for patients receiving radiation therapy. **Table 3** provides recommendations for antiemetic prophylaxis for children receiving chemotherapy. Lastly, the guidelines recommend prophylaxis with metoclopramide for prevention of emesis in patients with advanced cancer (MASCC high level of consensus and moderate level of confidence, ESMO level of evidence: III, ESMO grade of recommendation: C). Other prophylaxis options are: haloperidol, levomepromazine (not available in the US) or olanzapine. In patients with malignant bowel obstruction, octreotide is recommended with a conventional antiemetic. If relief is suboptimal, then the use of an anticholinergic anti-secretory agent and/or corticosteroids is recommended in combination with the other agents or as an alternative. There was no evidence to support the use of antiemetics for opioid-induced nausea and vomiting.

Table 1. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
Non-AC highly emetic chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A

Non-AC highly emetic chemotherapy	Dexamethasone on days 2-4 in combination with the above	High/ moderate	I/B
Women with breast cancer receiving AC chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A
Women with breast cancer receiving AC chemotherapy	Dexamethasone should be given on days 2-3 with the above except if fosaprepitant, netupitant or rolapitant were used on day 1	Moderate/ moderate	II/B
Olanzapine Use – prophylaxis of delayed nausea and in prevention of acute symptoms	Olanzapine may be appropriate, especially for nausea, with a 5-HT3 RA plus dexamethasone	Low/ low	II/B
Prevention of acute emesis in MEC	5-HT3 RA plus dexamethasone	Moderate/ moderate	II/B
Prevention of delayed emesis in patients receiving MEC with known potential for delayed emesis	Dexamethasone on days 2-3	Low/ moderate	III/C
Prevention of delayed emesis in patients receiving MEC	No routine prophylaxis	No confidence possible/ high	IV/D
Prevention of carboplatin-induced acute nausea and vomiting	NK1 RA, dexamethasone and 5-HT3 RA	Moderate/ moderate	II/B
Prevention of carboplatin-induced delayed nausea and vomiting	If fosaprepitant, netupitant or rolapitant were used on day 1 then no antiemetic prophylaxis is required. If aprepitant is given on day 1 then aprepitant should be given on days 2-3	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin acute nausea and vomiting prevention	5-HT3 RA plus dexamethasone plus aprepitant	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin delayed nausea and vomiting prevention	Dexamethasone is recommended	Moderate/ moderate	II/B
Prevention of nausea and vomiting with low or minimal emetogenic chemotherapy	A single regimen of dexamethasone or 5-HT3 RA or a dopamine RA (e.g., metoclopramide) may be considered	No confidence possible/ moderate	II/B
Prevention of nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Prevention of delayed nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Treatment of breakthrough nausea and vomiting	Use of an antiemetic with a different mechanism of action than that of the antiemetic used for prophylaxis Olanzapine 10 mg orally for 3 days is recommended	Moderate/ moderate	II/B
Anticipatory nausea and vomiting	Benzodiazepines are recommended	Moderate/moderate	II/A
Anticipatory nausea and vomiting	Behavioral therapies including: progressive muscle relaxation training, systematic desensitization and hypnosis	Moderate/moderate	II/B

High-dose chemotherapy for stem cell transplant	Combination of 5-HT3 RA with dexamethasone and aprepitant (124 mg on day 1 and 80 mg on days 2-4)	High/high	I/A

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); AC-anthracycline-cyclophosphamide; MEC – moderately emetogenic chemotherapy; NK1 RA – neurokinin 1 receptor antagonist (aprepitant, fosaprepitant, netupitant, rolapitant)

Table 2. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Radiotherapy.[6]

Emetic Risk Level	Area of Treatment	Antiemetic Guideline	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High	Total body irradiation	Prophylaxis with a 5-HT3 RA and dexamethasone	High/high Moderate/high - for addition of dexamethasone	II/B IIIC – for addition of dexamethasone
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT3 RA and optional dexamethasone	High/high Moderate/high – for the addition of dexamethasone	II/A II/B - for the addition of dexamethasone
Low	Cranium	Prophylaxis or rescue with dexamethasone	Low/high	IV/D
Low	Head and neck, thorax region and pelvis	Prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist or a 5-HT3 RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with dexamethasone, a dopamine receptor antagonist or 5-HT3	Low/high	IV/D
Concomitant chemotherapy	Any area	Follow recommendations for antiemetic prophylaxis for chemotherapy regimen unless the RT regimen has a higher emetic risk and then treatment recommendation should be followed according to the highest risk	Low/high	IV/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); RT – radiation therapy

Table 3. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Children Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High emetic risk chemotherapy	5-HT3 RA plus dexamethasone plus aprepitant	High/high	II/B
High emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
High emetic risk chemotherapy and patient is unable to receive aprepitant	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
Low emetic risk chemotherapy	5-HT3 RA	Moderate/moderate	II/B
Minimal emetic risk chemotherapy	No antiemetic prophylaxis is recommended	Moderate/high	V/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, tropisetron, palonosetron)

MASCC/ESMO Anticipatory Nausea and Vomiting in Adults and Children Receiving Chemotherapy

In 2016, the MASCC/ESMO updated their 2011 recommendations on the treatment of patients with anticipatory nausea and vomiting who are receiving chemotherapy.[5] Evidence was graded as described in the MASCC/ESMO guideline above. An updated literature search was performed with the following inclusion criteria: full text primary studies; published in English; evaluated an intervention for the treatment of nausea and vomiting; the outcome of complete control was measured; and included at least 10 participants. No new literature was found meeting the inclusion criteria. Previous recommendations of optimizing acute and delayed phase nausea and vomiting control for prevention of anticipatory nausea and vomiting were reiterated (MASCC moderate confidence and high consensus and ESMO level of evidence III and grade A). Behavioral therapies and benzodiazepines can also be considered for treatment.

MASCC/ESMO Recommendations for Prevention of Nausea and Vomiting Following Multi-Day Chemotherapy, High-dose Chemotherapy and Breakthrough Nausea and Vomiting

Multiple day chemotherapy regimens, high-dose chemotherapy and breakthrough nausea and vomiting are conditions that require specialized management for the prevention of nausea and vomiting.[7] In the recent MASCC/ESMO recommendations, updated evidence on antiemetic treatment options for patients with these conditions included two new RCTs. Guideline development utilized the IDSA and Scientific Confidence methodology described above. Changes from the previous recommendations included olanzapine for breakthrough pain and the use of aprepitant for multiple-day regimens and high-dose regimens. Recommendations for prevention of nausea and vomiting are as follows:

- In the acute phase receiving multiple-day cisplatin chemotherapy
    - 5-HT3 RA, dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- In the delayed phase receiving multiple-day cisplatin chemotherapy
    - Dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- Breakthrough

- Olanzapine 10 mg daily for three days (moderate confidence/moderate consensus and ESMO level II/B)[7]

- High-dose chemotherapy for stem cell transplant
  - 5-HT3 RA, dexamethasone and aprepitant (high confidence/high consensus and ESMO level I/A)[7]

New Formulations:

A new extended-release granisetron (ERG) injection (Sustol®) was approved in 2016 for the use in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens.[8] ERG injection should be given as a 10 mg subcutaneous (SQ) dose at least 30 minutes before the start of emetogenic chemotherapy on Day 1. ERG injection should not be given more than once every 7 days and for not more than 6 months in patients receiving successive emetogenic chemotherapy cycles.

ERG 10 mg SQ was approved based on one clinical trial comparison to palonosetron 0.25 mg IV.[8] The trial was a multi-center, double-blind, parallel group study in patients with cancer undergoing treatment with MEC or anthracycline plus cyclophosphamide combination chemotherapy. A single dose of each agent, in combination with IV dexamethasone 8 mg or 20 mg, was given 30 minutes prior to chemotherapy on Day 1. The study population (n=733) was 63% Caucasian and 79% female with a mean age of 57 years. MEC was given to 55% of patients and 45% received combination therapy with anthracycline and cyclophosphamide. The primary endpoint was the percent of patients obtaining a complete response (defined as no emetic episodes and no rescue medication use) in the acute phase (within 24 hours) and the delayed phase (>24 to 120 hours) following chemotherapy. A complete response was demonstrated in 166 (83%) of patients receiving ERG and in 183 (89%) of patients receiving palonosetron in the acute phase receiving MEC.[8] In the delayed phase, ERG was associated with a complete response in 137 (69%) of patients and in 144 (70%) in palonosetron treated patients.[8] In patients receiving anthracycline and cyclophosphamide, there was a complete response rate in the acute phase in 120 (70%) of patients receiving ERG and 99 (64%) of patients receiving palonosetron. ERG was associated with 85 (50%) of patients treated with ERG obtaining a complete response compared to 74 (47%) in the palonosetron group during the delayed phase. ERG was shown to be non-inferior, but not superior, to palonosetron.

The most common adverse reactions are injection site reactions, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia and gastrointestinal reflux. Hypersensitivity reactions have occurred up to 7 days or longer after an ERG injection.

Additional RCTs are presented below and abstracts are available in **Appendix 3**.

Table 4. Description of Randomized Comparative Clinical Trials for Extended-Release Granisetron.

Study	Comparison	Population	Primary Outcome	Results
Raftopoulos, et al[11] RCT, DB, MC, Phase 3, non-inferiority	ERG 5 mg SQ or ERG 10 mg SQ vs. Palonosetron 0.25mg IV One dose 30-60 min. prior to chemotherapy Both treatments were given with IV dexamethasone HEC regimens were also given oral dexamethasone 8 mg twice daily on days 2-4	Adults with confirmed malignancy and scheduled to receive MEC or HEC during first cycle N=1,341	The percentage of patients obtaining a complete response in the acute and delayed phase (no emetic episodes and no use of rescue medication during acute and delayed phase)	<u>MEC Acute Phase</u> ERG 5 mg: 160 (74.8%) ERG 10 mg: 163 (76.9% Palonosetron: 156 (75.0%) ERG 5 mg vs. Palonosetron: P = 1.0 ERG 10 mg vs. Palonosetron: P = 0.73 <u>MEC Delayed Phase</u> ERG 5 mg: 110 (51.4%) ERG 10 mg: 124 (58.5%) Palonosetron: 119 (57.20%) ERG 5 mg vs. Palonosetron: P = 0.24 ERG 10 mg vs. Palonosetron: P = 0.84 <u>HEC Acute Phase</u> ERG 5 mg: 178 (77.7%) ERG 10 mg: 195 (81.3%) Palonosetron: 192 (80.7%) ERG 5 mg vs. Palonosetron: P = 0.49 ERG 10 mg vs. Palonosetron: P = 0.91 <u>HEC Delayed Phase</u> ERG 5 mg: 143 (62.4%) ERG 10 mg: 161 (67.1%) Palonosetron: 153 (64.3%) ERG 5 mg vs. Palonosetron: P = 0.70 ERG 10 mg vs. Palonosetron: P = 0.56 • CI not provided for results
Schnadig, et al[12] RCT, DB, DD, PG, MC, Phase 3	ERG 10 mg SQ vs. Ondansetron 0.15 mg/kg IV Both treatments were given with dexamethasone 12 mg IV and fosaprepitant 150 mg IV. Regimens were also given oral	Adults with confirmed malignancy scheduled to receive highly emetogenic chemotherapy receiving their first cycle	Delayed phase (24-120 hours) complete response (no emesis or rescue medication)	ERG 10 mg: 291 (64.7%) Ondansetron: 256 (56.6%) ARR 8.0% (95% CI, 1.7 to 14.4) P = 0.014

	dexamethasone 8 mg once daily on day 2 and twice daily on days 3-4.	N = 450		
Boccia, et al[13] RCT, MC, DB, PC, PG, Phase 3	<u>Cycle 1</u> ERG 5 mg SC or ERG 10 mg SC vs. Palonosetron 0.25 mg IV <u>Cycle 2-4</u> ERG 5 mg SC vs. ERG 10 mg SC Both treatments were given with IV dexamethasone	Adults with confirmed malignancy receiving MEC or HEC N = 1,395	Complete response (no emetic episodes, no rescue medication) of ERG 10 mg during acute (0-24 hours) and delayed (>24-120 hours) phases during chemotherapy cycles 2-4	<u>Complete Response HEC Acute Phase</u> ERG 10 mg cycle 1: 81.3% ERG 10 mg cycle 4: 87.8% Palonosetron cycle 1: 75% <u>Complete Response HEC Delayed Phase</u> ERG 10 mg cycle 1: 67.1% ERG 10 mg cycle 4: 83.1% Paonosetron cycle 1: 81% * Results for palonosetron cycle 4 were not provided.

Abbreviations: ARR = actual risk reduction; DB = double-blind; DD = double-dummy; ERG = extended-release granisetron; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; SQ = subcutaneous.

<u>Doxylamine/Pyridoxine (Bonjesta)</u>

A new extended-release, fixed dose formulation of the currently available doxylamine/pyridoxine was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[9] The combination product is 20 mg doxylamine and 20 mg pyridoxine to be given as one tablet at bedtime on Day 1. If symptoms are not adequately controlled on Day 2, then the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum dosage is 2 tablets a day.

The extended-release doxylamine/pyridoxine formulation was not studied in clinical trials. The approval was based on a clinical trial of doxylamine 10 mg/pyridoxine 10 mg (Diclegis) formulation that has been previously reviewed.[9] A pharmacokinetic crossover trial of 48 women found extended-release doxylamine 20 mg/pyridoxine 20mg to be bioequivalent to two combination tablets of 10 mg doxylamine and 10 mg pyridoxine. A second multi-dose, crossover trial found bioequivalence of one ER doxylamine 20 mg/pyridoxine 20 mg tablet given twice daily to one tablet of doxylamine 10 mg/pyridoxine 10 mg given three times daily.

<u>Aprepitant Use in Pediatrics</u>

In 2015, aprepitant (Emend) was approved for pediatric use (ages 12 to 17 years and for patients less than 12 years who weight at least 30 kg) for the prevention of chemotherapy-induced acute and delayed nausea and vomiting in combination with other antiemetic agents for patients receiving initial and repeat MEC or

HEC (including cisplatin) regimens.[10] The dose for pediatric patients is the same as for adults, 125 mg aprepitant on day 1 and 80 mg on days 2 and 3. The study used for the pediatric indication is presented below.

Table 5. Description of Randomized Comparative Clinical Trials for Aprepitant.

Study	Comparison	Population	Primary Outcome	Results
Kang, et al[14] RCT, MC, Phase 3, DB	Aprepitant* vs. Placebo† * Aprepitant 125 mg orally for 12-17 years; 3.0 mg/kg (maximum 125 mg) orally for ages 6 mo. to <12 years and ondansetron on day 1. On day 2 and 3, aprepitant 80 mg for ages 12-17 years and 2.0 mg/kg (max 80 mg) for ages 6 months to <12 years. Ondansetron was given on day 1 according to manufacturer recommendations. † Oral placebo and ondansetron were given on day 1. Placebo only was given on days 2 and 3. Ondansetron dosing was based on manufacturer's recommendation. *† Dexamethasone IV was allowed for both groups	Patients 6 months to 17 years with documented malignancy receiving MEC or HEC N = 307	The proportion of patients who obtained a complete response (no vomiting, retching or use of rescue medications) in the delayed phase (25-120 hours post chemotherapy)	<u>Delayed phase</u> Aprepitant: 77 (51%) Placebo: 39 (26%) ARR: 25%; P < 0.0001

Abbreviations: ARR = actual risk reduction; DB = double-blind; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; RCT = randomized clinical trial.

New FDA Safety Alerts:
No safety alerts identified.

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Appendix 1: Current Preferred Drug List

Antiemetics, 5HT3 and Substance P Antagonists

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SOLUTION	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	SOLUTION	ZOFRAN	ONDANSETRON HCL	Y
ORAL	TAB RAPDIS	ONDANSETRON ODT	ONDANSETRON	Y
ORAL	TAB RAPDIS	ZOFRAN ODT	ONDANSETRON	Y
ORAL	TABLET	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	TABLET	ZOFRAN	ONDANSETRON HCL	Y
INTRAVEN	VIAL	EMEND	FOSAPREPITANT DIMEGLUMINE	N
ORAL	CAP DS PK	EMEND	APREPITANT	N
ORAL	CAPSULE	AKYNZEO	NETUPITANT/PALONOSETRON HCL	N
ORAL	CAPSULE	EMEND	APREPITANT	N
ORAL	FILM	ZUPLENZ	ONDANSETRON	N
ORAL	TABLET	ANZEMET	DOLASETRON MESYLATE	N
ORAL	TABLET	GRANISETRON HCL	GRANISETRON HCL	N
ORAL	TABLET DR	DICLEGIS	DOXYLAMINE/PYRIDOXINE HCL	N
TRANSDERM	PATCH TDWK	SANCUSO	GRANISETRON	N
ORAL	TABLET	VARUBI	ROLAPITANT	N
ORAL	TABLET	BONJESTA	DOXYLAMINE/PYRIDOXINE	N
INTRAVEN	VIAL	ALOXI	PALONOSETRON	
SUBCUTA	VIAL	SUSTOL	GRANISETRON	N

Appendix 2: New Comparative Clinical Trials

A total of 151 citations were manually reviewed from the initial literature search. After further review, 149 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Navari, et al[15] RCT, DB, Phase 3	Olanzapine 10 mg* vs. Placebo* * Given on days 1-4 Both groups received dexamethasone, aprepitant or fosaprepitant and a 5-hydroxy-tryptamine type 3-recetptor antagonist	Adult patients with malignant disease naïve to chemotherapy receiving cisplatin or cyclophosphamide-doxarubicin N=380	Nausea prevention (defined as zero on a visual analog scale for nausea) during the overall assessment (0-120 hours), the early assessment period (0-24 hours) and the later assessment period (25-120 hours)	<u>No nausea 0-24 hours</u> Olanzapine: 135 (74%) Placebo: 82 (45%) ARR: 29%; P = 0.002 <u>No nausea 25-120 hours</u> Olanzapine: 75 (42%) Placebo: 45 (25%) ARR: 17%; P = 0.002 <u>No nausea 0-120 hours</u> Olanzapine: 66 (37%) Placebo: 39 (22%) ARR: 15%; P = 0.002
Kovács, et al [16] MC, DB, DD, RCT, Phase 3	IV Palonosetron 10 mcg/kg* or IV Palonosetron 20 mcg/kg* vs. IV Ondansetron 150 mcg/kg given as 3 doses 4 hours apart on day 1 * Given up to 4 cycles on day 1	Pediatric patients (0-17 years) scheduled to receive MEC or HEC for treatment of malignant disease N=502	Complete response (no vomiting, retching or rescue drug treatment) during the acute phase (0-24 hours post-chemotherapy) during the first cycle of chemotherapy	<u>Complete Response</u> Palonosetron 10 mcg/kg: 90 (54%) Palonosetron 20 mcg/kg: 98 (59%) Ondansetron: 95 (59%) <u>Palonosetron 20 mcg/kg vs. Ondansetron</u> WSD 0.36% (97.5% CI, -11.7 to 12.4) P = 0.0022 (non-inferiority achieved) <u>Palonosetron 10 mcg/kg vs. Ondansetron</u> WSD -4.41% (97.5% CI, -16.4 to 7.6) P = NS

Abbreviations: ARR = absolute risk reduction; DB = double-blind; DD=double-dummy; IV = intravenous; MC = multi-center; RCT = randomized clinical trial; WSD = weighted sum of the difference

Appendix 3: Abstracts of Comparative Clinical Trials

Randomized phase III trial of APF530 versus palonosetron in the prevention of chemotherapy-induced nausea and vomiting in a subset of patients with breast cancer receiving moderately or highly emetogenic chemotherapy
Boccia R, Cooper W, Boyle E

Background
APF530 provides controlled, sustained-release granisetron for preventing acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). In a phase III trial, APF530 was noninferior to palonosetron in preventing acute CINV following single-dose moderately (MEC) or highly emetogenic chemotherapy (HEC) and delayed CINV in MEC (MEC and HEC defined by Hesketh criteria). This exploratory subanalysis was conducted in the breast cancer subpopulation.
Methods
Patients were randomized to subcutaneous APF530 250 or 500 mg (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg during cycle 1. Palonosetron patients were randomized to APF530 for cycles 2 to 4. The primary efficacy end point was complete response (CR, no emesis or rescue medication) in cycle 1.
Results
Among breast cancer patients (*n* = 423 MEC, *n* = 185 HEC), > 70 % received anthracycline-containing regimens in each emetogenicity subgroup. There were no significant between-group differences in CRs in cycle 1 for acute (APF530 250 mg: MEC 71 %, HEC 77 %; 500 mg: MEC 73 %, HEC 73 %; palonosetron: MEC 68 %, HEC 66 %) and delayed (APF530 250 mg: MEC 46 %, HEC 58 %; 500 mg: MEC 48 %, HEC 63 %; palonosetron: MEC 52 %, HEC 52 %) CINV. There were no significant differences in within-cycle CRs between APF530 doses for acute and delayed CINV in MEC or HEC in cycles 2 to 4; CRs trended higher in later cycles, with no notable differences in adverse events between breast cancer and overall populations.
Conclusions
APF530 effectively prevented acute and delayed CINV over 4 chemotherapy cycles in breast cancer patients receiving MEC or HEC.

Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial
Raftopoulos H, Cooper W, O'Boyle, et al

Purpose
Subcutaneous APF530 provides controlled sustained release of granisetron to prevent acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). This randomized, double-blind phase 3 trial compared APF530 and palonosetron in preventing acute and delayed CINV after moderately (MEC) or highly emetogenic chemotherapy (HEC).
Methods
Patients receiving single-day MEC or HEC received single-dose APF530 250 or 500 mg subcutaneously (SC) (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg. Primary objectives were to establish APF530 noninferiority to palonosetron for preventing acute CINV following MEC or HEC and delayed CINV following MEC and to determine APF530 superiority to palonosetron for preventing delayed CINV following HEC. The primary efficacy end point was complete response (CR [using CI difference for APF530 − palonosetron]). A lower confidence bound greater than −15 % indicated noninferiority.

Results
In the modified intent-to-treat population (MEC = 634; HEC = 707), both APF530 doses were noninferior to palonosetron in preventing acute CINV after MEC (CRs 74.8 % [−9.8, 9.3] and 76.9 % [−7.5, 11.4], respectively, vs. 75.0 % palonosetron) and after HEC (CRs 77.7 % [−11.5, 5.5] and 81.3 % [-7.7, 8.7], respectively, vs. 80.7 % palonosetron). APF530 500 mg was noninferior to palonosetron in preventing delayed CINV after MEC (CR 58.5 % [−9.5, 12.1] vs. 57.2 % palonosetron) but not superior in preventing delayed CINV after HEC. Adverse events were generally mild and unrelated to treatment, the most common (excluding injection-site reactions) being constipation.
Conclusions
A single subcutaneous APF530 injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC.

APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy
Schnadig I, Agajanian R, Dakhil C, et al

AIM
APF530, extended-release granisetron, provides sustained release for ≥5 days for acute- and delayed-phase chemotherapy-induced nausea and vomiting (CINV). We compared efficacy and safety of APF530 versus ondansetron for delayed CINV after highly emetogenic chemotherapy (HEC), following a guideline-recommended three-drug regimen.
METHODS
HEC patients received APF530 500 mg subcutaneously or ondansetron 0.15 mg/kg intravenously, with dexamethasone and fosaprepitant. Primary end point was delayed-phase complete response (no emesis or rescue medication).
RESULTS
A higher percentage of APF530 versus ondansetron patients had delayed-phase complete response (p = 0.014). APF530 was generally well tolerated; treatment-emergent adverse event incidence was similar across arms, mostly mild-to-moderate injection-site reactions.
CONCLUSION
APF530 versus the standard three-drug regimen provided superior control of delayed-phase CINV following HEC.

Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.
Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM.

BACKGROUND:
Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in paediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children.
METHODS:
In this final analysis of a phase 3, randomised, multicentre, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12-17 years; 3·0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12-17 years; 2·0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on

day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomisation was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for paediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25-120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530.
FINDINGS:
Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase ($p<0{\cdot}0001$). The most common grade 3-4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group vs 21 [14%] of 150 in the control group), anaemia (14 [9%] vs 26 [17%]), and decreased neutrophil count (11 [7%] vs 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group vs 22 [15%] in the control group).
INTERPRETATION:
Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy.
FUNDING:
Merck & Co., Inc.

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting.
Navari RM, Qin R, Ruddy KJ, et al

BACKGROUND:
We examined the efficacy of olanzapine for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy.
METHODS:
In a randomized, double-blind, phase 3 trial, we compared olanzapine with placebo, in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-hydroxytryptamine type 3-receptor antagonist, in patients with no previous chemotherapy who were receiving cisplatin (≥70 mg per square meter of body-surface area) or cyclophosphamide-doxorubicin. The doses of the three concomitant drugs administered before and after chemotherapy were similar in the two groups. The two groups received either 10 mg of olanzapine orally or matching placebo daily on days 1 through 4. Nausea prevention was the primary end point; a complete response (no emesis and no use of rescue medication) was a secondary end point.
RESULTS:
In the analysis, we included 380 patients who could be evaluated (192 assigned to olanzapine, and 188 to placebo). The proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine than with placebo in the first 24 hours after chemotherapy (74% vs. 45%, P=0.002), the period from 25 to 120 hours after chemotherapy (42% vs. 25%, P=0.002), and the overall 120-hour period (37% vs. 22%, P=0.002). The complete-response rate was also significantly increased with olanzapine during the three periods: 86% versus 65% (P<0.001), 67% versus 52% (P=0.007), and 64% versus 41% (P<0.001), respectively. Although there were no grade 5 toxic effects, some patients receiving olanzapine had increased sedation (severe in 5%) on day 2.

CONCLUSIONS:
Olanzapine, as compared with placebo, significantly improved nausea prevention, as well as the complete-response rate, among previously untreated patients who were receiving highly emetogenic chemotherapy. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT02116530.).

Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study.
Kovács G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova E.
BACKGROUND:
Palonosetron has shown efficacy in the prevention of chemotherapy-induced nausea and vomiting in adults undergoing moderately or highly emetogenic chemotherapy. We assessed the efficacy and safety of palonosetron versus ondansetron in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients.
METHODS:
In this multicentre, multinational, double-blind, double-dummy, phase 3 study, paediatric patients aged between 0 and younger than 17 years, who were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease were randomised centrally (1:1:1) to receive up to four cycles of 10 μg/kg or 20 μg/kg palonosetron on day 1, or three 150 μg/kg doses of ondansetron on day 1, scheduled 4 h apart, according to a static central permuted block randomisation scheme by an interactive web response system. Randomisation was stratified according to age and emetogenicity. Treatment allocation was masked to project team members involved in data collection and analysis, and members of the investigator's team. The primary endpoint was complete response (no vomiting, retching, or use of rescue drugs) during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle, as assessed in the population of randomly assigned patients who received moderately or highly emetogenic chemotherapy and an active study drug. The primary efficacy objective was to show the non-inferiority of palonosetron versus ondansetron during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle through comparison of the difference in the proportions of patients who achieved a complete response with palonosetron (πT) minus ondansetron (πR) versus a preset non-inferiority margin (δ -15%). To be considered as non-inferior to ondansetron, for at least one of the doses of palonosetron, the lower limit of the 97·5% CI for the weighted sum of the differences in complete response rates had to be superior to -15%. Safety was assessed, according to treatment received. This study is registered with ClinicalTrials.gov, number NCT01442376, and has been completed.
FINDINGS:
Between Sept 12, 2011, and Oct 26, 2012, we randomly assigned 502 patients; 169 were assigned to receive 10 μg/kg palonosetron, 169 to receive 20 μg/kg palonosetron, and 164 to receive 3 × 150 μg/kg ondansetron, of whom 166, 165, and 162, respectively, were included in the efficacy analysis. In the acute phase, complete responses were recorded in 90 (54%) patients in the 10 μg/kg palonosetron group, 98 (59%) in the 20 μg/kg palonosetron group, and 95 (59%) in the ondansetron group. Non-inferiority versus ondansetron was shown for 20 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates 0·36% [97·5% CI -11·7 to 12·4]; p=0·0022). Non-inferiority versus ondansetron was not shown for 10 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates -4·41% [97·5% CI -16·4 to 7·6]). In the first on-study treatment cycle, treatment-emergent adverse events were reported in 134 (80%) of 167 patients who received 10 μg/kg palonosetron, 113 (69%) of 163 who received 20 μg/kg palonosetron, and 134 (82%) of 164 who received ondansetron. The most common drug-related treatment-emergent adverse events were nervous system disorders, mainly headache, which occurred in three (2%) patients who received 10 μg/kg palonosetron, one (<1%) patient who received 20 μg/kg palonosetron, and two (1%) patients who received ondansetron. The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26%]) than in the 10 μg/kg palonosetron group (52 [31%]) and the ondansetron group (55 [34%]).

INTERPRETATION:
Non-inferiority was shown for 20 µg/kg palonosetron during the acute phase of the first on-study chemotherapy cycle. 20 µg/kg palonosetron is now indicated by the European Medicines Agency and the US Food and Drug Administration for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients aged 1 month to younger than 17 years.
FUNDING:
Helsinn Healthcare.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to March Week 5 2017
Search Strategy:

#	Searches	Results
1	rolapitant.mp.	24
2	(netupitant and palonosetron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	34
3	ondansetron.mp. or Ondansetron/	2880
4	fosaprepitant.mp.	58
5	aprepitant.mp.	634
6	dolasetron.mp.	251
7	granisetron.mp. or Granisetron/	1093
8	(doxylamine and pyridoxine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	83
9	palonosetron.mp.	375
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	4474
11	limit 10 to (english language and humans and yr="2015 -Current")	296
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	151

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs will be subject to PA criteria

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for doxylamine/pyridoxine (Diclegis®) or (Bonjesta) for pregnancy-related nausea or vomiting?	**Yes:** Go to #4	**No:** Go to #5

4. Has the patient failed a trial of pyridoxine? Message: • Preferred vitamin B products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Approve for up to 3 months	**No:** Pass to RPh; deny and recommend a trial of pyridoxine.
5. Is the request for dronabinol (Marinol®)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have anorexia associated with HIV/AIDS?	**Yes:** Approve for up to 6 months*	**No:** Go to #7
7. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	**Yes:** Approve for up to 6 months*	**No:** Go to #8
8. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months*	**No:** Go to #9
9. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	**Yes:** Approve for up to 6 months*	**No:** Pass to RPh. Deny; medical appropriateness. Must trial at least 2 preferred antiemetics.
* If the request is for dronabinol (Marinol®) do not exceed 3 doses/day for 2.5 mg and 5 mg strengths and 2 doses/day for the 10 mg strength.		

P&T / DUR Review: *7/17 (KS); 1/17 (DM) 1/16; 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03*
Implementation: *TBD; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03*

Trade Name (generic)	
Trulance™ (plecanatide)	Indication not funded
Indications	
Plecanatide is indicated in adults for the treatment of chronic idiopathic constipation (CIC)	
Dosage	
3 mg tablet taken orally once daily, with or without food	
Background	
Plecanatide is a guanylate cyclase-C (GC-C) receptor agonist that acts on the luminal surface of the intestinal epithelium. GC-C receptor activation results in increased cGMP, which stimulates chloride and bicarbonate secretion into the intestinal lumen. This leads to increased intestinal fluid and accelerated intestinal transit.[1]	
Efficacy	
FDA approval of plecanatide was based on two identically designed, 12-week, double-blind, placebo-controlled, randomized, multicenter, phase 3 clinical trials in 1775 adult patients with CIC who were randomized 1:1 to either placebo or plecanatide 3 mg once daily.[1] The study populations had a mean age of 45 years (range 18 to 80 years) and were 80% female, 72% white, and 24% black. Included were subjects who met modified Rome III functional constipation diagnostic criteria for ≥3 months before screening, with symptom onset for ≥6 months before diagnosis. Modified Rome III criteria required that patients report <3 defecations/week, rarely have a loose stool without laxative use, not manually facilitate defecations, and not meet criteria for irritable bowel syndrome with constipation. Also, patients were required to report at least two of the following symptoms for ≥25% of defecations: straining, lumpy or hard stool, sensation of incomplete evacuations, or sensation of anorectal obstruction/blockage. Consistency of stools was rated with a validated, pictorial, 7 point Bristol Stool Form Scale (BSFS). A score of 1 indicated hard lumps ranging up to 7, which was a watery stool. Patients also had to demonstrate the following during the two-week pre-treatment assessment period: <3 spontaneous (i.e., without laxative use) bowel movements associated with a sense of complete evacuation (CSBM) per week; BSFS of 6 or 7 in <25% of spontaneous bowel movements; and BSFS of 1 or 2 in ≥25% of defecations or a straining value recorded on ≥25% of days when a BM was reported or ≥25% of BMs resulting in a sense of incomplete evacuation. Plecanatide demonstrated efficacy over placebo for response rate (primary endpoint), with a responder defined as a patient who had ≥3 CSBMs in the same week for ≥9 weeks out of the 12-week treatment period and ≥3 of the last 4 weeks of the study:	

	Plecanatide 3 mg	Placebo	Difference (95% CI, p-value)	NNT
Response rate study 1	21% (n=453)	10% (n=452)	11% (6.1 to 15.4, p<0.005)	10
Response rate study 2	21% (n=430)	13% (n=440)	8% (2.6 to 12.4, p<0.005)	13

The difference in the mean change in CSBMs/week frequency (from baseline to week 12) between plecanatide group and placebo group was about a 1.1 CSBMs/week.
Safety
Black box warning: Risk of serious dehydration in pediatric patients; contraindicated in patients less than 6 years of age; avoid use in patients 6 to 17 years old; and safety and effectiveness not established in patients less than 18 years of age **Common adverse reactions:** Diarrhea **Contraindications:** Patients who are <6 years of age, due to the risk of serious dehydration, and patients who have known or suspected mechanical gastrointestinal obstruction **Warnings and precautions:** Severe diarrhea may occur. Also, same as black box warning above.
Evidence Gaps/Limitations
No studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.
Recommendation
Restrict use for OHP-funded conditions through Prior Authorization. Add plecanatide to “Drugs for Constipation” PA criteria.
References
1.Trulance (plecanatide) tablets [prescribing information]. New York, NY. Synergy Pharmaceuticals, Inc.; January 2017.

Trade Name (generic)

Symproic® (naldemedine) | Indication not funded

Indications

Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Dosage

0.2mg orally once a day with or without food.

Background

Naldemedine is an opioid antagonist structurally related to naltrexone and has received Schedule II controlled substance labeling by the U.S. Drug Enforcement Administration (DEA). The removal of the controlled substance scheduling is currently being petitioned by Shionogi Incorporated, the manufacturer of naldemedine.

Efficacy

The FDA approval of naldemedine was based on data from two studies: COMPOSE I and COMPOSE II.COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies.[1]A third study, COMPOSE III, is an ongoing, 52-week, randomized, double-blind, placebo-controlled, long-term safety study.[2] The studies have not yet been published but are available for review at clinicaltrials.gov.[2-4] COMPOSE I and COMPOSE II evaluated naldemedine in the treatment of adults using opioids to managed chronic non-cancer pain with OIC. The primary endpoint was the proportion of responders who had a positive response in 9 out of the 12 week treatment period. Positive response was defined as at least 3 spontaneous bowel movements (SBMs) per week and an increase from baseline of at least 1 SBM per week. Results from both studies are presented in **Table 1**.

Table 1: Efficacy Responder Rates in COMPOSE I and II in Patients with OIC and Chronic Non-Cancer Pain[2]

	COMPOSE I			**COMPOSE II**		
	Naldemedine 0.2 mg once daily (n = 273)	Placebo (n = 272)	Treatment Difference (95% CI; p-value)	Naldemedine 0.2 mg once daily (n = 276)	Placebo (n = 274)	Treatment Difference (95% CI; p-value)
Proportion of Responders	48% (130/273)	35% (94/273)	13% (5 to 21%; p=0.002)	53% (145/276)	34% (92/274)	19% (11 to 27%; p<0.0001)
Mean change in SBMs/week from baseline to Weeks 11-12	3.1	2.0	1.0 (0.6 to 1.5; p-value not reported)	3.3	2.1	1.2 (0.8 to 1.7; p-value not reported)

Safety

Contraindications:

- Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation.
- Patients with a history of a hypersensitivity reaction to naldemedine.

Warnings and Precautions:

- Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with naldemedine.
- Avoid use with strong CYP3A inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's Wort) because it may reduce the efficacy of naldemedine.
- Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. Naldemedine should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Evidence Gaps/Limitations

Long term safety data has been collected over 52 weeks, but not published. No studies found to support evidence for treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization. Add naldemedine to “Drugs for Constipation” PA criteria.

References

1. Symproic (Naldemedine) Prescribing Information. Florham Park, NJ. Shionogi, March 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208854s000lbl.pdf. Accessed April 5, 2017.
2. Efficacy and Safety of Naldemedine in the Treatment of Opioid-induced Constipation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01965158?term=naldemedine&rank=3. Accessed April 6, 2017.

3. Efficacy and Safety of Naldemedine in Treating Opioid-induced Constipation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01993940?term=naldemedine&rank=2. Accessed April 6, 2017.
4. Long Term Safety of Naldemedine - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01965652?term=naldemedine&rank=1. Accessed April 6, 2017.