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Drug Class Update: Agents for Inflammatory Bowel Diseases (oral, rectal)

Date of Review: October 2024

Date of Last Review: Sept 2015
Dates of Literature Search: 08/01/2015 – May 23, 2024

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

Purpose for Class Update:
The oral and rectal medications approved to manage inflammatory bowel diseases (IBDs) were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the September 2015 meeting. This review will evaluate evidence published since 2015 to ensure Oregon Health Authority (OHA) policies are consistent with current guideline recommendations.

Plain Language Summary:
- This review looks at recently published literature for treatment of ulcerative colitis (UC) and Crohn's disease (CD) with oral and rectal medicines.
- Crohn's disease and UC are lifelong conditions of the digestive tract that cause swelling and irritation in the intestines. Ulcerative colitis affects the large intestine (colon) and rectum. Crohn's disease can affect the entire digestive tract, but usually affects the small intestine and beginning of the large intestine. Symptoms of both conditions include diarrhea, abdominal discomfort, bloody bowel movements, weight loss, fatigue, and fever. People have periods of active disease with symptoms (relapse) and periods when the symptoms disappear (remission) with both conditions.
- Treatment for mild UC is one of the medicines known as 5 aminosalicylic acids (5-ASAs), which help control swelling and irritation. The four 5-aminosalicylic acid medicines approved by the Food and Drug Administration (FDA) include balsalazide, olsalazine, sulfasalazine and mesalamine. These medicines can be taken by mouth (oral) or used rectally as an enema or suppository. Side effects reported with 5-ASA medicines include heartburn, nausea, diarrhea, and headache. There is no new evidence that one of the 5-ASAs is better than another for improving symptoms of UC.
- Treatment for mild CD includes short term use (up to 2 months) of steroids such as prednisone or budesonide to help calm swelling and irritation and cause remission, which is a time when the symptoms disappear. After finishing a course of steroids, medicines to suppress the immune system are started to prevent the immune system from attacking healthy cells and prevent relapse. Examples of immune suppressors include azathioprine, mercaptopurine, and methotrexate. These medicines may increase the chance of getting sick from an infection and can cause liver damage so people must be closely followed by their doctor when taking these medicines.
- Since this class was last reviewed, 2 new budesonide products have been approved by the FDA for conditions other than CD or UC. New evidence shows that:
    - When taken for 9 months, budesonide 4 mg caps were more effective than placebo for preventing kidney damage due to a buildup of a protein called immunoglobulin A in kidney cells. This protein builds up and causes swelling that can make it harder for the kidneys to work. The most

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common side effects of budesonide in people with kidney disease included high blood pressure, fluid accumulation (edema), muscle spasms, acne, increased weight, shortness of breath, heartburn, and fatigue.
    - Budesonide oral suspension was more effective than placebo over 12 weeks for relieving symptoms of eosinophilic esophagitis. The esophagus is the swallowing tube that runs from the throat to the stomach. Eosinophilic esophagitis is caused by an overreaction of the immune system which causes swelling and irritation of the esophagus. This causes heartburn and trouble swallowing. The most common side effects of budesonide in people with eosinophilic esophagitis included infections, headache, and throat irritation.
- Mesalamine capsules, tablets, enemas and suppositories are preferred by the OHA and providers can prescribe these medicines without submitting documentation to the OHA. Other preferred products include oral forms of balsalazide, sulfasalazine and olsalazine. Prednisone and budesonide capsules are also preferred by the OHA. If the provider chooses a non-preferred medicine, they must explain to the OHA why their patient needs this medicine. This process is called prior authorization. We recommend the 2 new budesonide products be designated as non-preferred with prior authorization criteria.

Research Questions:

1. What is the comparative evidence for efficacy of azathioprine, balsalazide, budesonide, mesalamine, thiopurines (i.e., azathioprine, mercaptopurine), methotrexate, olsalazine, and sulfasalazine for inducing and maintaining remission of CD or UC?
2. Are there any differences in harms for azathioprine, balsalazide, budesonide, mesalamine, thiopurines, methotrexate, olsalazine, and sulfasalazine for inducing and maintaining remission of CD or UC?
3. Do the included drugs differ in their effectiveness or harms for managing CD or UC based on age, race, ethnicity, gender, or patients with comorbidities?

Conclusions:

- Since the last P & T Committee review, 9 systematic reviews evaluating conventional oral and rectal therapy for UC[1-5] and CD[6-9] were published. Five clinical practice guidelines for medical treatment of UC in adults,[10,11] CD in adults[12,13] and CD in pediatrics[14] have been updated.

Ulcerative Colitis Systematic Reviews

- An April 2022 Cochrane review evaluated the efficacy and safety of tacrolimus for induction of remission in people with corticosteroid-refractory UC.[1] The randomized controlled trials (RCTs) were small with missing data sets, short follow-up, and the clinical endpoints used were not in line with those suggested by regulatory bodies.[1] Based on the low-quality evidence presented in this systematic review, it is difficult to draw clinical conclusions regarding the safety and efficacy of tacrolimus for inducing remission in UC.[1]
- An August 2020 Cochrane review assessed the efficacy, dose-responsiveness and safety of oral 5-ASA products (i.e., mesalamine, olsalazine, balsalazide) compared to sulfasalazine for induction of remission in patients with mild-to-moderate UC.[2] There is moderate-quality evidence that 5-ASA products are not more effective than sulfasalazine in inducing clinical remission on patients with mild-to-moderate UC.[2] High-quality evidence suggests 5-ASA dosed once daily appears to be as efficacious as conventionally-dosed 5-ASA (2 to 3 times a day).[2] There does not appear any difference in efficacy or safety among the various 5-ASA formulations (high-quality evidence).[2]
- A second August 2020 Cochrane review evaluated the efficacy, dose-responsiveness, and safety of oral 5-ASA products (i.e., mesalamine, olsalazine, balsalazide) compared to sulfasalazine for maintenance of remission in quiescent UC and compared the efficacy and safety of once-daily dosing of oral 5-ASA with conventional (2 to 3 times per day) dosing regimens.[3] There is high-quality evidence that 5-ASA products are superior to placebo for maintaining remission in people with mild-to-moderate UC.[3] High-quality evidence shows 5-ASA products are inferior compared to sulfasalazine for maintaining remission.[3] High-quality evidence showed no difference between 5-ASA products and placebo, and 5-ASA products and sulfasalazine in commonly reported adverse effects (AEs).[3] Oral 5-ASA administered once daily has a similar benefit and harm profile as conventional dosing for maintenance of remission in patients with quiescent UC (high-quality evidence).[3]

- A May 2016 Cochrane review assessed the effectiveness and safety of azathioprine and mercaptopurine for maintaining remission of UC.[4] Azathioprine appears to be more effective than placebo for maintenance of remission in UC (low-quality evidence).[4] Azathioprine or mercaptopurine may be effective as maintenance therapy for patients who have failed or cannot tolerate mesalamine or sulfasalazine and for patients who require repeated courses of steroids (very low-quality evidence).[4]
- An August 2015 Cochrane review assessed the efficacy and safety of methotrexate for maintenance of remission in patients with UC.[5] Three RCTs (n=165) met inclusion critiera.[5] The results for efficacy and safety outcomes between methotrexate and placebo, methotrexate and sulfasalazine, methotrexate and 6-mercaptopurine and methotrexate and 5-ASA were uncertain.[5] There is no high-quality evidence supporting the use of methotrexate for maintenance of remission in ulcerative colitis.[5]

Crohn's Disease Systematic Reviews

- A June 2019 Cochrane review evaluated evidence for the safety and efficacy of 5-ASA products for maintenance of surgically induced remission in CD.[6] The 5-ASA preparations are superior to placebo for the maintenance of surgically induced clinical remission in patients with CD (moderate-quality evidence).[6] The sulfasalazine class of 5-ASA agents failed to demonstrate superiority against placebo and 5-ASA products failed to demonstrate superiority compared to no treatment (very low- and low-quality evidence, respectively).[6] The efficacy of two different doses of the same 5-ASA product and the efficacy of 5-ASA compared to thiopurines (azathioprine or mercaptopurine) in maintaining surgically induced remission of CD remains unclear.[6] Thiopurines lead to more serious AEs and discontinuation due to AEs (low-quality evidence) .[6] The 5-ASA formulations appear to be safe with no difference in the occurrence of AEs or withdrawals due to AEs when compared with placebo or no treatment (low-quality evidence).[6]
- An August 2019 Cochrane review evaluated the benefits and harms of azathioprine and mercaptopurine to maintain remission in adults with CD who had undergone surgery to remove diseased portions of their intestine.[7] Moderate-quality evidence suggests that azathioprine and mercaptopurine may be superior to placebo for maintenance of surgically induced remission in participants with CD.[7] There was no clear difference in the number of clinical relapses when thiopurines were compared with 5-ASA agents (low-quality evidence).[7] There was very low-quality evidence that azathioprine and mercaptopurine are more likely to result in more serious adverse effects (SAEs) and withdrawals due to an AE (low-quality evidence) when compared to 5-ASA agents.[7]
- A July 2016 Cochrane review evaluated the efficacy of 5-ASAs compared to placebo, corticosteroids, and other aminosalicylates for the treatment of mild to moderate active CD.[8] In a pooled analysis of 3 RCTs, sulfasalazine was not superior to placebo for inducing remission at 17 to 26 weeks of follow-up (moderate-quality evidence).[8] Sulfasalazine is inferior to corticosteroids for the treatment of mild to moderate active CD (moderate-quality evidence).[8] Olsalazine and low dose mesalamine (1 to 2 grams/day) are not superior to placebo for induction of remission (low-quality evidence). High dose mesalamine (3.2 to 4 grams/day) is not more effective than placebo for inducing response or remission (low-quality evidence) in mild to moderate CD.[8]
- A September 2016 Cochrane review assessed the efficacy and safety of oral 5-ASA agents for the maintenance of medically induced remission in CD.[9] Moderate-quality evidence to suggests there is no difference between oral 5-ASA preparations and placebo for the maintenance of medically induced remission in patients with CD.[9]

Ulcerative Colitis Clinical Practice Guidelines

- Most of the evidence used in the 2022 European Crohn's and Colitis Organization guidance is from randomized controlled trials (RCTs) of adults with UC.[10] Strong recommendations for oral and rectal 5-ASA products, steroids, and thiopurines (conventional therapy) for induction and maintenance of remission in UC are summarized below. Additional recommendations based upon moderate- to low-quality evidence are presented in **Table 2**.
    - 5-ASA products at a dose of ≥ 2 grams/day are recommended to induce remission in patients with mild to moderate, active UC (strong recommendation; low-quality evidence).[10]
    - Topical (rectal) 5-ASA is recommended at a dose of ≥ 1 gram/day for the induction of remission in active distal colitis (strong recommendation, low-quality evidence).[10]

- Topical (rectal) steroids are recommended for the induction of remission in patients with active distal colitis (strong recommendation, very low-quality evidence).[10]
- The use of oral 5-ASA at a dose ≥2 gram/day is recommended for maintenance of remission in mild to moderate, active UC (strong recommendation; very low-quality evidence).[10]
- Monotherapy with thiopurines is recommended for the maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-ASA (strong recommendation, moderate-quality evidence).[10]
- Oral prednisolone is recommended for induction of remission in non-hospitalized patients with moderate to severe, active UC (strong recommendation; very low-quality evidence).[10]

- The American Gastroenterological Association (AGA) published recommendations on the management of mild to moderate UC in 2019.[11] Strong recommendations for conventional therapy are summarized below. Additional recommendations based upon moderate to low-quality evidence are presented in **Table 3**.
  - AGA supports use of standard-dose mesalamine (2 to 3 grams/day) or diazo-bonded 5-ASAs (balsalazide or olsalazine) rather than low-dose mesalamine (< 2 grams/day), sulfasalazine, or no treatment for induction and maintenance of remission in patients with extensive mild- to moderate-UC (strong recommendation; moderate-quality evidence).[11]

Crohn's Disease Clinical Practice Guidelines

- In 2019 European Crohn's and Colitis Organization published guidance for the medical management of adults with CD.[12] Additional recommendations are summarized in **Table 4**.
  - The use of 5-ASA for induction of remission of CD is not recommended (weak recommendation, moderate-quality evidence).[12]
  - Budesonide is effective for the induction of remission in patients with mild-to-moderate CD (strong recommendation, moderate-quality evidence).[12]
  - In patients with active, moderate-to-severe CD, the use of systemic corticosteroids is suggested for the induction of clinical response and remission (weak recommendation, strong-quality evidence).[12]
  - The use of oral 5-ASA products is not recommended for maintenance of medically induced remission in patients with CD (strong recommendation, low-quality evidence).[12]
  - Thiopurines are recommended for the maintenance of remission in patients with steroid-dependent CD (strong recommendation, moderate-quality evidence).[12]
  - Methotrexate administered parenterally is recommended for the maintenance of remission in patients with steroid-dependent CD disease (weak recommendation, moderate-quality evidence).[12]
- American Gastroenterological Association guidance published in 2021 addresses the medical management of moderate to severe luminal and fistulizing CD.[13] In adult outpatients with moderate to severe CD, the AGA recommends the use of TNF-antagonists (infliximab, adalimumab, or certolizumab pegol) over no treatment for induction and maintenance of remission.[13] Thiopurines and methotrexate are suggested for use as combination therapies with TNF-antagonists for induction and maintenance of remission compared to TNF-antagonist monotherapy.[13] The use of thiopurines for induction of remission, corticosteroids for maintenance of remission and the use of mesalamine for induction or maintenance of remission are not recommended due to overall lack of efficacy.[13] For moderate to severe CD, the AGA panel suggests the early introduction of a biologic with or without an immunomodulator rather than delaying their use until after failing mesalamine and/or corticosteroids.[13] **Table 5** presents the AGA recommendations for conventional immunosuppressants (thiopurines, methotrexate, prednisone, and budesonide) for treatment of moderate to severe CD.
- Guidance published by the Canadian Association of Gastroenterology in 2019 provides recommendations for medical management of pediatric CD.[14] There is sparse evidence for the use of conventional therapies in children, so many recommendations are based upon low- to very low-quality evidence.

- The CAG guidance suggests corticosteroid therapies, including prednisone for moderate to severe pediatric CD (conditional recommendation, very low-quality evidence).[14]
- Use of oral 5-ASA is not recommended for induction of clinical remission (conditional recommendation, very low-quality evidence) or maintenance therapy in pediatric patients with moderate disease (strong recommendation; very low-quality evidence).[14]
- Thiopurines are not recommended for induction therapy (strong recommendation, very low-quality evidence) and corticosteroids are not recommended for maintenance therapy (strong recommendation, low-quality evidence) in pediatric CD.[14]

- There was insufficient evidence to determine if thiopurines, steroids, or 5-ASA products differ in their effectiveness or harms for managing CD or UC based on age, race, ethnicity, gender, or comorbidities.
- New formulations and expanded indications that received Food and Drug Administration (FDA) approval include:
  - April 2016: budesonide capsules indication expanded to mild to moderate CD involving the ileum and/or ascending colon for children 8 years and older.[15]
  - June 2020: mesalamine delayed release tablets indication expanded to treatment of mild to moderate, active UC in pediatric patients weighing at least 24 kg.[16]
  - December 2021: TARPEYO (budesonide) 4 mg targeted-release capsules were approved to reduce proteinuria in adults with primary Immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.[17] In December 2023 the initial indication was expanded to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression.[18]
  - February 2024: EOHILA (budesonide) oral suspension received approval for 12 weeks of treatment in adult and pediatric patients aged 11 years of age and older with eosinophilic esophagitis.[19]
- New FDA safety warnings are described in **Table 7**.

Recommendations:

- Based on clinical review of the evidence, no changes to the OHA Preferred Drug List (PDL) are recommended for the drug class of oral and rectal agents for IBD.
- Make budesonide 4 mg delayed release capsules (TARPEYO) non-preferred to ensure appropriate utilization in people with IgAN at risk for kidney disease progression and recategorize to “Glucocorticoids, oral” class on PDL.
- Make budesonide oral suspension (EOHILIA) non-preferred with PA criteria to ensure appropriate utilization in people with eosinophilic esophagitis (see **Appendix 3**) and recategorize to “Glucocorticoids, oral” class on PDL.
- After review of costs in executive session, mesalamine DR tablets (both strengths) were made preferred.

Summary of Prior Reviews and Current Policy:

- The P & T Committee last reviewed oral and rectal medications for management of mild-to-moderate inflammatory bowel diseases at the September 2015 meeting. At that time the committee recommended no changes to the preferred 5-ASA products on the Oregon Health Plan (OHP) Preferred Drug List (PDL). 5-aminosalicylic acid drugs approved in the United States for treatment of UC include sulfasalazine, balsalazide, olasalazine and mesalamine. At least one oral corticosteroid formulation was made available on the PDL for adjunctive management of mild CD. Due to limited short-term evidence, budesonide rectal foam was not designated as a preferred agent.
- Mesalamine capsules, tablets, enemas and suppositories are preferred by the OHA Other preferred 5-ASA products include oral forms of balsalazide, sulfasalazine and olsalazine. Prednisone and budesonide capsules are also preferred by the OHA. Nonpreferred products are subject to general PA criteria

for nonpreferred medications to ensure appropriate utilization for FDA-approved indications and conditions funded by the Health Evidence Review Commission (HERC). The current PDL status for oral and rectal formulations used to treat IBDs is presented in **Appendix 1**.

- In the second quarter (April to June) of 2024, 82% of utilization for IBD conventional therapy was for preferred products including mesalamine delayed release tablets, sulfasalazine, mesalamine suppositories, mesalamine capsules, balsalazide, and budesonide capsules. Approximately 18% of claims were processed for nonpreferred mesalamine capsule and tablet formulations.

Background:

Crohn's Disease and Ulcerative Colitis

Crohn's disease and UC are classified as IBDs and are most often diagnosed in adolescence and young adulthood.[20] Host genetic factors, gut microbiota, environmental factors and immune response contribute to development of CD and UC.[21] Crohn's disease is characterized by chronic, relapsing inflammation involving the full thickness of the gastrointestinal wall at any point from mouth to rectum, whereas UC is characterized by mucosal ulceration limited to the colon and rectum. Persistent inflammation can lead to intestinal scarring and further complications requiring surgery.[22] Symptoms of both conditions include blood and/or mucus in the stool, urgency, tenesmus, incontinence, increased frequency of bowel movements, and abdominal discomfort. Systemic symptoms include fatigue, weight loss, loss of appetite, anemia, inflammatory eye disease, sclerosing cholangitis, and arthritis. Once IBD is diagnosed, the goals of therapy consist of eliminating symptoms, normalizing quality of life, and preventing complications while minimizing the adverse effects of medications.[20] Unique considerations when treating children and adolescents with IBD include attention to the effects of the disease on growth and development, bone health, and psychosocial functioning.[20]

The initial presentation of UC is characterized by symptoms of an inflamed rectum, namely, bleeding, urgency, and tenesmus.[23] Ulcerative colitis may present at any age, but there is a predominant age distribution of onset that peaks between ages 15 and 30 years.[23] The pattern of disease activity is most often described as relapsing and remitting.[23] Patients with active UC are more likely to have comorbid psychological conditions of anxiety and depression and are more likely to have impaired social interactions or career progression.[23] Predictors of an aggressive disease course and colectomy include extensive disease, severe endoscopic activity (presence of large and/or deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids and elevated inflammatory markers.[24] Long-standing UC is also associated with colorectal cancer, which is believed to be related to long-standing unchecked inflammation.[23]

The incidence of CD is highest between age 10 and 30 years, but CD can present at any age.[25] The most common symptom of CD is chronic diarrhea, but some patients may not experience this symptom.[26] Abdominal pain, often localized to the right lower quadrant of the abdomen and worsened postprandially, is common.[26] Fatigue is also a very prevalent symptom in CD and is thought to arise from a number of factors including inflammation, anemia, or various vitamin and mineral deficiencies.[26] Some patients will present with constitutional signs or symptoms including fever, weight loss or, in the case of younger patients, growth failure.[26] Patients who have had CD for greater than 8 to 10 years have increased risk of colorectal cancer.[25] Contributors to severe disease include: large or deep mucosal lesions on endoscopy or imaging, presence of fistula and/or perianal abscess, presence of strictures, prior intestinal resections, particularly of segments > 40 cm, presence of a stoma, extensive disease (ileal involvement > 40 cm, or pancolitis), anemia, elevated C-reactive protein and low albumin.[13]

Diagnosis of UC and CD is based on history, physical examination, laboratory studies, and endoscopic evaluation.[27] The Montreal Classification is often used in CD clinical trials and classifies patients with CD based on age of diagnosis, location of disease, and disease phenotype (see **Table 1**).[28] Two separate scoring tools are used to assess disease activity in CD and UC. The Crohn's Disease Activity Score (CDAI) is an evaluation of 8 clinical factors involved in CD assessment, including number of soft stools per day, abdominal pain, general well-being, use of medications for diarrhea, presence of abdominal mass, hematocrit, and percentage deviation from standard weight. A total score of 450 or greater indicates extremely severe disease, a score of 150 or greater indicates active disease, and a score

less than 150 indicates minimal disease.[29] Therapeutic response is defined as decrease in CDAI ≥ 100 points.[29] The Mayo Clinic Score is used to evaluate UC symptoms.[22] Four subscores evaluate rectal bleeding, stool frequency, patient-reported outcomes, and endoscopy results. Each domain is scored from 0 to 3 points, with a higher score indicating more severe disease.[22] The total score can range from 0-12. A critical component of this score is the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered to have more severe UC regardless of the final score.[22] AGA guidance (2020) defines moderate to severe UC as a Mayo Clinic scores of 6–12 with an endoscopic subscore of 2 or 3.[24] A reduction of 3 points on the Mayo score constitute a clinically meaningful improvement in UC symptoms.[24] The domains for the CDAI and Mayo Clinic Score are presented in more depth in **Table 1.**

Table 1. Assessment of Disease Activity in Crohn's Disease and Ulcerative Colitis[28,30-32]

Outcome Measure	Domains	Scale and Scoring
Montreal Classification of Crohn's Disease	**Age at Diagnosis**: A1: ≤ 16 yo A2: 17-40 yo A3: Over 40 yo **Disease Location**: L1: Ileal L2: Colonic L3: Ileocolonic L4: Isolated Upper Gastrointestinal **Behavio**r: B1: Inflammatory: Nonstricturing/nonpenetrating B2: Stricturing B3: Penetrating **Modifier:** P: Perianal Disease	• Used to describe stages of Crohn's Disease
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 x 2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x 5) 3. General well-being (subjective score of 0-4) for 1 week (weight x 7) 4. Presence of complications (weight x 20) 5. Use of diphenoxylate/atropine or opiates for diarrhea (weight x 30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x 10) 7. Absolute deviation of hematocrit from 47% (men) or 42% (women) (weight x 6) 8. Percentage deviation from standard weight (weight x 1)	Each factor is weighted and summed to achieve a total score. • Scores ≤150 indicate minimal disease (remission) • Scores 151 to 220 indicate mild to moderate disease • Scores 221-450 indicate moderate to severe disease • Scores >450 indicate extremely severe disease • Therapeutic response is defined as decrease in CDAI ≥ 100 points

Mayo Clinic Score for Grading Activity of Ulcerative Colitis	**Assessment** **Points** **1.Stool Frequency** -Patient reporting a normal number of daily stools 1 -3-4 more stools than normal 2 -≥ 5 more stools than normal 3 **2. Rectal Bleeding** -None 0 -Blood streaks seen with stool less than half the time 1 -Blood with most stools 2 -Pure blood passed 3 **3.Endoscopic Findings** -Normal or inactive colitis 0 -Mild friability, erythema, decreased vascularity 1 -Friability, marked erythema, absent vascular pattern, erosions 2 -Ulcerations and spontaneous bleeding 3 **4. Physician Global Assessment** -Normal 0 -Mild colitis 1 -Moderate colitis 2 -Severe colitis 3	The score can range from 0-12 with higher scores indicating increasing severity. A critical component of this score is the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score. A reduction of 3 points on the Mayo score constitute a clinically meaningful improvement in UC symptoms. 1

The choice of therapy for UC considers the level of disease activity (mild, moderate, or severe), the extent of the disease (proctitis, left-sided disease, extensive disease, or pancolitis), and patient preferences.[33] The primary goal of treatment is endoscopically confirmed healing of the mucosa.[34] First-line therapies for induction and maintenance of remission in mild to moderate UC are 5-ASA formulations including sulfasalazine, mesalamine, olsalazine, and balsalazide.[11] Sulfasalazine is composed of 5-ASA linked to sulfapyridine via a diazo bond.[3] This bond is readily cleaved by bacterial azo-reductases in the colon to yield the two components.[3] Of these, 5-ASA is the therapeutically active component, while sulfapyridine, which is primarily absorbed into systemic circulation, is assumed to function solely as a carrier molecule.[3] The branded mesalamine product, ASACOL, consists of a pellet of 5-ASA destined for release in the terminal ileum or colon due to a coating that dissolves at a pH greater than 7.0.[3] Another branded mesalamine formulation, PENTASA, is a microsphere formulation that consists of 5-ASA microgranules enclosed within a semi-permeable membrane of ethylcellulose.[3] It is designed for controlled release that begins in the duodenum and continues into the affected regions of the lower bowel.[3] Olsalazine (DIPENTUM) consists of two 5-ASA molecules linked by a diazo bond.[3] Other formulations, such as balsalazide, are composed of 5-ASA molecules azo-bonded to various benzoic acid derivatives.[3] Like sulfasalazine, these compounds are poorly absorbed in the upper digestive tract but are readily metabolized by the intestinal flora in the lower bowel.[3] A fourth mesalamine formulation, LIALDA, uses Multi Matrix System (MMX) technology to delay and extend delivery of active drug throughout the colon.[3]

Moderate-to-severe UC may require oral corticosteroids for induction of remission and as a bridge to targeted immune modulator (TIM) medications that sustain remission. Glucocorticoids (budesonide, prednisolone) are highly effective in the acute treatment of UC, but they should only be used for short intervals, due to their AEs.[34] The 2020 American Gastroenterological Association guidelines recommend the use of TIMs for treating moderate to severe, active UC in

adults whose disease has responded inadequately to conventional therapy including aminosalicylates, corticosteroids, azathioprine or mercaptopurine.[35] Continuation of these agents is only recommended if there is clear evidence of response.[35]

Clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extra intestinal manifestations when choosing a treatment strategy.[25] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease is distinguished from preventing relapse (maintaining remission).[29] The immunosuppressants azathioprine, mercaptopurine, and methotrexate have been used for many years to treat CD but because of slow onset of action they are typically used to maintain remission.[25] Aminosalicylates such as mesalamine have been evaluated in a number of studies but have not been shown to effectively induce or maintain remission in CD.[25] Some data indicates sulfasalazine may be modestly effective for induction of remission in colonic CD, but it has not been shown to maintain remission.[25] Steroids are used to induce remission but are not effective maintenance agents.[25] Multiple steroid formulations have been used in CD including prednisone and budesonide.[25] Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used to treat CD due to insufficient evidence demonstrating efficacy.[29]

In pregnant patients with IBD, corticosteroid use may increase the risk of gestational diabetes and adverse pregnancy outcomes and should not be considered a reasonable maintenance therapy during pregnancy.[36] Due to its teratogenic effects, methotrexate needs to be stopped at least 3 months before conceiving.[36] Based on available data and balancing the risk to pregnancy of active disease, biologics and thiopurines used in the treatment of IBD are considered low risk during pregnancy and breastfeeding.[36]

Indications for 2 New Budesonide Formulations: Eosinophilic Esophagitis and IgA Nephropathy

All oral budesonide products are currently categorized in the IBD class based on historical indications for oral budesonide. However, two new budesonide formulations, not indicated for IBD, have recently received FDA approval for use in eosinophilic esophagitis and IgAN. Evidence for the approval for these products is summarized in the New Formulations section below.

Eosinophilic Esophagitis

EOHILA oral suspension received FDA approval for 12 weeks of treatment in adult and pediatric patients aged 11 years of age and older with eosinophilic esophagitis (EoE).[19] Eosinophilic esophagitis is a chronic immune-mediated disorder in which eosinophils are found in esophageal mucosa in response to various stimuli or antigens.[37] Altered epithelial permeability can lead to an environment that enhances antigen presentation, which in turn leads to recruitment of eosinophils.[38] In a recent study, 63.5% of patients with eosinophilic esophagitis also had a diagnosis of either asthma, allergic rhinitis, atopic dermatitis, or food allergies, with 3% having all 4 diagnoses.[39] The patient-reported Dysphagia Symptom Questionnaire (DSQ) is a 3-question daily diary that has been validated for the measurement of dysphagia frequency and severity in patients with eosinophilic esophagitis.[40,41] Scores can range from 0 to 84, with higher values indicating more frequent and severe dysphagia.[41] A DSQ score of 0 represents an absence of dysphagia symptoms.[41] The minimal clinically important difference (MCID) has been estimated as a change of 6.5 points in the DSQ score.[41]

Budesonide oral suspension is the second FDA-approved agent for EoE. Dupilumab also has FDA-approval to manage EoE in adults and pediatric patients aged 1 year and older (see **Appendix 3** for PA criteria).[42] The evidence for the use of dupilumab in EoE was reviewed by the P & T Committee at the October 2022 meeting. Current therapies for EoE include off-label use of proton pump inhibitors (PPIs), off-label use of locally applied corticosteroid preparations, dietary therapy with amino acid formula or empiric food elimination, and endoscopic dilation.[43] While high quality studies are not available to determine the best course of therapy for EoE, PPI therapy is usually initiated based on expert consensus, cost, and ease of therapy.[44] The 2020 American Gastroenterological Association (AGA) and the Joint Task Force (JTF) on Allergy-Immunology Practice Parameters clinical guideline for the management of EoE suggests the use of PPIs over no

treatment as a conditional recommendation based on very low-quality evidence.[45] Based on their longstanding safety profile and ease of administration, patients may prefer to start with PPI therapy and dietary restrictions before initiating a corticosteroid.[45]

When PPI therapy is not effective, inhaled corticosteroid preparations administered locally to the esophagus have been prescribed.[46] Although it has not been approved by the FDA, fluticasone administered locally as a spray from a metered-dose inhaler or a viscous preparation of budesonide (e.g., Pulmicort Respules for inhalation) are primarily used for treatment of eosinophilic esophagitis.[47-50] The efficacy of these medications applied locally to the esophagus in improving symptoms and histologic abnormalities after 2 to 12 weeks of use ranges from 53% to 95%.[48,50] The AGA/JTF guideline strongly recommends locally applied corticosteroids over no treatment based on moderate-quality evidence.[45] In short-term studies of 3 months or less, no increased risk of adverse events was observed in patients treated with topically applied corticosteroids compared with placebo (RR 1; 95% CI, 0.85 to 1.19), although local viral and fungal infections and very limited description of adrenal suppression have been described in certain populations.[45] A conditional recommendation based on moderate-quality evidence suggests locally applied corticosteroids are preferred over systemic administration of oral corticosteroids, due to the increased risk of adverse events observed with systemic corticosteroid therapy.[45]

IgA Nephropathy

TARPEYO 4 mg targeted-release capsules were initially approved by the FDA with an indication to reduce proteinuria in adults with primary IgA nephropathy (IgAN) at risk of rapid disease progression in December 2021.[17] In December 2023 the initial indication was expanded to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression.[18] It is the only FDA-approved product for these indications. IgA nephropathy is the most prevalent primary chronic glomerular disease worldwide.[51] All patients with IgAN should receive optimized supportive care, which consists of reduction of proteinuria with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker (ARB), blood pressure control, treatment of dyslipidemia, and lifestyle modification (such as dietary sodium and protein restriction, smoking cessation, weight control, and exercise as appropriate).[51]

Patients with IgAN who are at high risk of disease progression (ie, proteinuria ≥1 g/day despite at least three to six months of optimized support should generally receive immunosuppressive therapy.[52] Immunosuppressive therapy (ie, systemic glucocorticoids) likely improves short-term kidney outcomes among patients with IgAN but has the potential for significant toxicity if given in high doses.[52] Prednisone, methylprednisolone, and budesonide dosing regimens have been studied in patients with IgAN.[52] In December 2023, the National Institute for Health and Care Excellence (NICE) published guidance for the use of targeted-release budesonide in the treatment of IgA.[53] The recommendations support the use of targeted-release budesonide to treat IgAN when there is rapid disease progression in adults with a urine protein-to-creatinine ratio of 1.5 grams/gram or more as an add-on to optimize standard care including the highest tolerated dose of ACE inhibitors or ARBs, unless these are contraindicated.[53] Targeted-release budesonide is formulated with the expectation that it is mainly released in the terminal ileum.[53] It reduces IgA production at this site and is not absorbed systemically to the same extent as other glucocorticoids.[53]

Methods:

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

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

New Systematic Reviews:

Induction and Maintenance of Remission in Ulcerative Colitis

Cochrane: Tacrolimus For Induction of Remission in Corticosteroid-Refractory Ulcerative Colitis

An April 2022 Cochrane review evaluated the efficacy and safety of tacrolimus for induction of remission in people with corticosteroid-refractory UC.[1] This publication updated a previous 2008 Cochrane systematic review. Literature was searched through October 2021 to identify relevant RCTs.[1] The primary outcomes were induction of remission and clinical improvement, while secondary outcomes included rates of AEs and serious adverse effects (SAEs). Five RCTs (n=347) with a duration of 2 to 8 weeks met inclusion criteria.[1] Intravenous (IV), rectal, and oral formulations of tacrolimus were compared to placebo, cyclosporine, and beclomethasone.[1] All 5 RCTs were assessed as having a high risk of bias.[1] The RCTs were small, with missing data sets, offered short follow-up and the clinical endpoints used were not in line with those suggested by regulatory bodies.[1]

Tacrolimus (oral and rectal) may be superior to placebo (oral and rectal) in achieving clinical remission (17% tacrolimus versus 2% placebo; RR 3.76; 95% CI 1.03 to 13.73; p=0.05; 3 studies; low-quality evidence).[1] Tacrolimus may be superior to placebo for clinical improvement (52% tacrolimus versus 11% placebo; RR 4.47; 95% CI 2.15 to 9.29; p<0.0001; 3 studies; low-quality evidence).[1] There was no difference between tacrolimus and placebo on incidence of AEs (52% tacrolimus versus 48% placebo; RR 1.18; 95% CI 0.91 to 1.54; p=0.22; 3 studies; low-quality evidence).[1] The evidence showed no difference between tacrolimus compared to placebo on rates of SAEs (2% tacrolimus versus 0% placebo; RR 2.44; 95% CI 0.12 to 48.77; p=0.06; 3 studies; very low-quality of evidence).[1]

One study (n=113) compared oral tacrolimus to IV cyclosporine, with an intervention lasting 2 weeks.[1] The evidence showed no significant difference between tacrolimus and cyclosporine on achievement of clinical remission (45% tacrolimus versus 30% cyclosporine; RR 1.52; 95% CI 0.92 to 2.50; p=0.10; very low-quality evidence). The evidence showed no significant difference between tacrolimus and cyclosporine in achieving clinical improvement (70% tacrolimus versus 78% cyclosporine; RR 0.90; 95% CI 0.70 to 1.16; p=0.41; very low-quality evidence).[1] The study did not report rates of AEs or SAEs.[1]

One study (n=88) compared tacrolimus suppositories with beclomethasone suppositories over 4 weeks.[1] No difference in achievement of clinical remission was observed between tacrolimus and beclomethasone (36.4% tacrolimus versus 34% beclomethasone; RR 1.07; 95% CI 0.60 to 1.88; p=0.82; low-quality evidence).[1] No difference in clinical improvement was reported when comparing tacrolimus suppositories to beclomethasone suppositories (50% tacrolimus versus 50% beclomethasone; RR 1.00; 95% CI 0.66 to 1.52; p=1.00; low-quality evidence).[1] No significant difference in AEs was reported between tacrolimus compared with beclomethasone (47% tacrolimus versus 32% beclomethasone; RR 1.50; 95% CI 0.88 to 2.55; p=0.14; low-certainty evidence).[1] No difference in SAEs was observed when comparing tacrolimus to beclomethasone (2% tacrolimus versus 0% beclomethasone; RR 3.00; 95% CI 0.13 to 71.70; p=0.50; low-certainty evidence).[1]

In summary, based on the low-quality evidence presented in this systematic review, it is difficult to draw clinical conclusions regarding the safety and efficacy of tacrolimus in inducing remission in UC.[1] This review highlights the need for further research that targets the relevant clinical questions, uses appropriate trial methodology and reports key findings in a systematic manner that facilitates future integration of findings with current evidence to better inform clinicians.[1] Future studies need to be adequately powered and of sufficient duration to capture the efficacy and effectiveness of tacrolimus remission induction in UC.[1]

Cochrane: Oral 5-Aminosalicylic Acid for Induction of Remission in Ulcerative Colitis

An August 2020 Cochrane review assessed the efficacy, dose-responsiveness and safety of oral 5-ASA products (i.e., mesalamine, olsalazine, balsalazide) compared to placebo or sulfasalazine for induction of remission in patients with mild-to-moderate UC.[2] Literature was searched through June 11, 2019 for RCTs which enrolled adults with active UC.[2] Outcomes included: failure to induce clinical remission, clinical improvement, endoscopic improvement, adherence, AEs, and SAEs.[2] Four comparisons were analyzed: 5-ASA versus placebo, 5-ASA versus sulfasalazine, 5-ASA once-daily dosing versus conventional dosing (2 to 3 times a day), and head to head comparisons of different 5-ASA formulations.[2] Fifty-four RCTs studies (n=9612) met inclusion criteria.[2] Most studies were at low risk of bias.[2] Five studies were rated as having a high risk of bias due to incomplete outcome data and lack of blinding.[2] For the purposes of this class update only the comparative evidence between different products will be presented.

No differences in clinical remission rates between 5-ASA and sulfasalazine were reported in pooled data from 8 RCTs (n=526).[2] Fifty-four percent of 5-ASA-treated patients failed to enter remission compared to 58% of sulfasalazine-treated patients (RR 0.90, 95% CI 0.77 to 1.04; I^2 = 0%; moderate-quality evidence).[2] Fourteen studies (n=1053) reported failure to induce global or clinical improvement (including remission).[2] Thirty-seven percent of 5-ASA-treated patients failed to improve compared to 47% of sulfasalazine-treated patients (RR 0.88, 95% CI 0.76 to 1.01; I^2 = 0%; high-quality evidence).[2] Two RCTs did not show significant differences in complete endoscopic remission between 5-ASA and sulfasalazine.[2] The results were not pooled as each study used difference indices to measure endoscopic remission.[2] Six studies (n=362) provided data on failure to induce endoscopic improvement (including remission).[2] Forty-one percent of the 5-ASA-treated group failed to improve endoscopically compared to 45% of the sulfasalazine-treated group (RR 0.82, 95% CI 0.65 to 1.02; I^2 = 0%; moderate-quality evidence).[2]

Twelve studies (n=909) reported the proportion of participants who experienced at least one AE.[2] For 10 RCTs the inclusion criteria included tolerance of sulfasalazine.[2] Sulfasalazine-treated patients were significantly more likely than 5-ASA-treated patients to experience an AE.[2] Fourteen percent of the 5-ASA group experienced at least one AE compared to 29% of the sulfasalazine group (RR 0.48, 95% CI 0.36 to 0.63; I^2 = 0%; moderate-quality evidence).[2] Common AEs included flatulence, abdominal pain, nausea, diarrhea, headache and worsening UC.[2] Two studies (n=107) reported on the proportion of participants who experienced at least one SAE, and no difference was reported between the 5-ASA and sulfasalazine groups.[2] Six percent of participants in the 5-ASA group experienced an SAE compared to 4% of sulfasalazine group (RR 1.36, 95% CI 0.28 to 6.52; low-quality evidence.[2] Reported SAEs included erythematous rash, venous thrombosis, carcinoma, acute pancreatitis, rheumatoid arthritis, and erythema nodosum.[2]

There was no difference in remission rates between once-daily dosing and conventional dosing of 5-ASA in 5 RCTs (n=1761).[2] Sixty percent of once-daily participants failed to enter clinical remission compared to 61% of conventionally-dosed participants (RR 0.99, 95% CI 0.93 to 1.06; I^2 = 0%; high-quality evidence).[2] Eight percent of patients dosed once daily did not adhere to their medication regimen compared to 6% of conventionally-dosed patients (RR 1.36, 95% CI 0.64 to 2.86; n=358, 2 RCTs; low-quality evidence).[2] There does not appear to be any difference in efficacy among the various 5-ASA formulations.[2] Fifty percent of patients in the 5-ASA group did not enter remission compared to 52% of patients in the comparator group (RR 0.94, 95% CI 0.86 to 1.02; n=1968, 11 RCTs; moderate-quality evidence).[2] There was no evidence of a difference in the incidence of AEs and SAEs between once-daily and conventionally-dosed 5-ASA and head to head 5-ASA formulation studies.[2]

In summary, this systematic review identified data to show there is moderate-certainty evidence that 5-ASA is not more effective than sulfasalazine in inducing clinical remission on patients with mild-to-moderate UC.[2] High-certainty evidence suggests 5-ASA dosed once daily appears to be as efficacious as conventionally-dosed 5-ASA.[2] There does not appear any difference in efficacy or safety among the various 5-ASA formulations (high-quality evidence).[2]

Cochrane: Oral 5-Aminosalicylic Acid for Maintenance of Remission in Ulcerative Colitis

Another August 2020 Cochrane review evaluated the efficacy, dose-responsiveness, and safety of oral 5-ASA (i.e., mesalamine, olsalazine, balsalazide) compared to placebo or sulfasalazine for maintenance of remission in quiescent UC and compared the efficacy and safety of once-daily dosing of oral 5-ASA with conventional (2 or 3 times daily) dosing regimens.[3] This version updated a previous 2012 Cochrane systematic review.[3] Literature was searched through June 11, 2019 for RCTs with a minimum treatment duration of 6 months in patients of any age with mild-to-moderate UC.[3] The primary outcome was the inability to maintain clinical or endoscopic remission.[3] Secondary outcomes included adherence, AEs, SAEs, withdrawals due to AEs, and withdrawals or exclusions after entry.[3] Trials were separated into four comparison groups: 5-ASA versus placebo, 5-ASA versus sulfasalazine, once-daily 5-ASA dosing versus conventional dosing, and head to head comparisons of different 5-ASA formulations [balsalazide, olasalazine, branded mesalamine (PENTASA)] versus other branded mesalamine products (ASACOL) .[3]

Forty-four RCTs (n=9967) met inclusion criteria.[3] Most studies were at low risk of bias.[3] Ten studies were at high risk of bias as 7 of these studies were single-blind and 3 were open-label.[3] Eight studies were placebo-controlled and 12 RCTs compared 5-ASA to sulfasalazine.[3] Twelve RCTs were maintenance of remission studies comparing once-daily dosing of 5-ASA with conventional dosing.[3] Six studies compared the efficacy and safety of various formulations of 5-ASA for maintenance treatment.[3] Ten trials were dose-ranging studies of oral 5-ASA products.[3] For the purposes of this class update only the comparative evidence between different products will be presented.

Twelve trials (n=1655) compared efficacy of sulfasalazine and 5-ASA. Sulfasalazine is more effective than 5-ASA for maintenance of remission.[3] Forty-eight percent of 5-ASA-treated patients relapsed at 6 to 18 months compared to 43% of sulfasalazine-treated patients (RR 1.14, 95% CI 1.03 to 1.27; high-quality evidence).[3] Adherence to study medication and SAEs were not reported for this comparison.[3] There was no difference between sulfasalazine and 5-ASA in AEs at 6 to 12 months follow-up (RR 1.07, 95% CI 0.82 to 1.40; 7 studies, n=1138; moderate-quality evidence).[3]

There is little or no difference in clinical or endoscopic remission rates between once-daily and conventionally dosed 5-ASA products.[3] Thirty-seven percent of once-daily participants relapsed over 12 months compared to 39% of conventional-dosing participants (RR 0.94, 95% CI 0.88 to 1.01; 10 studies, n=3910; high-quality evidence).[3] There was no difference in medication adherence rates.[3] Ten percent of participants in the once-daily group failed to adhere to their medication regimen compared to 8% of participants in the conventional-dosing group (RR 1.18, 95% CI 0.72 to 1.93; 9 studies, n=2306; moderate-quality evidence).[3] Three percent of participants in the once-daily group experienced a SAE compared to 2% of participants in the conventional-dose group at six to 12 months (RR 1.20, 95% CI 0.77 to 1.87; moderate-quality evidence). There was no difference in the incidence of AEs at 6 to 13 months' follow-up (RR 0.98, 95% CI 0.92 to 1.04; 8 studies, n=3497; high-quality evidence).[3] There was no difference in the efficacy of different 5-ASA formulations.[3] Forty-four percent of patients in one 5-ASA formulation relapsed at 6 to 18 months compared to 41% of patients in a different 5-ASA formulation comparator group (RR 1.08, 95% CI 0.91 to 1.28; 6 studies, n=707; low-quality evidence).[3]

In summary, there is high-quality evidence that 5-ASA is inferior compared to sulfasalazine for maintaining remission of UC.[3] There was no difference between 5-ASA and sulfasalazine in commonly reported AEs such as flatulence, abdominal pain, nausea, diarrhea, headache, and dyspepsia.[3] Oral 5-ASA administered once daily has a similar benefit and harm profile as conventional dosing for maintenance of remission in patients with quiescent UC.[3]

Cochrane: Azathioprine And Mercaptopurine for Maintenance of Remission in Ulcerative Colitis

A May 2016 Cochrane review assessed the effectiveness and safety of azathioprine and mercaptopurine for maintaining remission of UC.[4] This publication updated a prior 2012 review. Remission of UC was defined as mild or absent symptoms with complete discontinuation of corticosteroids, irrespective of the use

of prophylactic medication, and continuing evidence on sigmoidoscopy of an uninflamed or grade 1 mucosa.[4] Literature was searched through July 30, 2015 for RCTs of at least 12 months duration that compared azathioprine or mercaptopurine with placebo or standard maintenance therapy (e.g. mesalamine).[4] The primary outcome was failure to maintain clinical or endoscopic remission. Secondary outcomes included AEs and withdrawal due to AEs. Seven studies (n=302) met inclusion criteria.[4] The risk of bias was high in three of the studies due to lack of blinding.[4]

A pooled analysis showed azathioprine was significantly superior to placebo for maintenance of remission.[4] Forty-four percent of azathioprine patients failed to maintain remission compared to 65% of placebo patients (4 studies, n=232; RR 0.68; 95% CI 0.54 to 0.86; low-quality evidence).[4] Two trials that compared mercaptopurine to mesalamine, or azathioprine to sulfasalazine showed significant heterogeneity and thus were not pooled.[4] Fifty percent of mercaptopurine patients failed to maintain remission compared to 100% of mesalamine patients (1 study, n=22; RR 0.53; 95% CI 0.31 to 0.90; very low-quality evidence).[4] Fifty-eight percent of azathioprine patients failed to maintain remission compared to 38% of sulfasalazine patients (1 study, n=25; RR 1.52; 95% CI 0.66 to 3.50; very low-quality evidence).[4] One small study found that mercaptopurine was superior to methotrexate for maintenance of remission.[4] In the study, 50% of mercaptopurine patients and 92% of methotrexate patients were unable to maintain remission (1 study, n=26; RR 0.55; 95% CI 0.31 to 0.95; very low-quality evidence).[4] One very small study compared azathioprine with cyclosporine and found that there was no significant difference between patients who did not achieve remission on azathioprine (50%) or cyclosporine (62.5%) (1 study, n=16; RR 0.80; 95% CI 0.33 to 1.92; very low-quality evidence).[4]

When placebo-controlled studies were pooled with aminosalicylate-comparator studies to assess AEs, there was no statistically significant difference between azathioprine and control in the incidence of AEs.[4] Nine percent of azathioprine patients experienced at least one AE compared to 2% of placebo patients (5 studies, 257 patients; RR 2.82; 95% CI 0.99 to 8.01; low-quality of evidence).[4] Patients receiving azathioprine were at significantly increased risk of withdrawing due to AEs.[4] Eight percent of azathioprine patients withdrew due to AEs compared to 0% of control patients (5 studies, 199 patients; RR 5.43; 95% CI 1.02 to 28.75; very low-quality of evidence).[4] Adverse events related to study medication included acute pancreatitis (3 cases, plus 1 case on cyclosporine) and significant bone marrow suppression (5 cases).[4] Deaths, opportunistic infection, or neoplasia were not reported.[4]

In summary, azathioprine therapy appears to be more effective than placebo for maintenance of remission in UC (low-quality evidence).[4] Azathioprine or mercaptopurine may be effective as maintenance therapy for patients who have been unable to achieve remission or cannot tolerate mesalamine or sulfasalazine and for patients who require repeated courses of steroids (very low-quality evidence).[4] More research is needed to evaluate superiority over standard maintenance therapy, especially in the light of potential AEs from azathioprine.[4]

<u>Cochrane: Methotrexate For Maintenance of Remission in Ulcerative Colitis</u>

An August 2015 Cochrane Review assessed the efficacy and safety of methotrexate for maintenance of remission in patients with UC.[5] Literature was searched through June 16, 2014 for RCTs in which methotrexate was compared to placebo or an active comparator in patients with quiescent UC.[5] The primary outcome was the occurrence of clinical or endoscopic relapse and secondary outcomes included frequency and nature of AEs. Three RCTs (n=165) met inclusion critiera.[5]

One moderate-quality study (n=67) compared oral methotrexate (12.5 mg/week) to placebo, another low-quality RCT (n=72) compared oral methotrexate (15 mg/week) to mercaptopurine (1.5 mg/kg/day) or 5-ASA (3 gram/day), and a third study with an unclear risk of bias (n=26) compared methotrexate (15 mg/week) in combination with sulfasalazine (3 gram/day) to sulfasalazine monotherapy.[5] The placebo-controlled study found no statistically significant differences in the proportion of patients who maintained remission.[5] At 9 months, 36% of methotrexate patients maintained remission compared to 54% of placebo patients (RR 0.64; 95% CI 0.28 to 1.45; low-quality evidence).[5] The study comparing combination therapy to sulfasalazine found no statistically significant difference in the proportion of patients who maintained remission.[5] At 12 months, 100% of patients in the combination group maintained remission compared to 75% of

sulfasalazine patients (RR 1.32, 95% CI 0.94 to 0.86; very low-quality).[5] There were no statistically significant differences in maintenance of remission rates between methotrexate and mercaptopurine or between methotrexate and 5-ASA.[5] At 76 weeks, 14% of methotrexate patients maintained remission compared to 64% of mercaptopurine patients (RR 0.22; 95% CI 0.03 to 1.45; very low-quality evidence) and 0% of 5-ASA patients (RR 1.13; 95% CI 0.06 to 20.71; very low-quality evidence).[5] Adverse events were poorly reported in the 3 included studies and no conclusions can be drawn regarding the safety of methotrexate maintenance therapy in patients with quiescent UC.[5]

In conclusion, the results for efficacy and safety outcomes between methotrexate and placebo, methotrexate and sulfasalazine, methotrexate and mercaptopurine, and methotrexate and 5-ASA were uncertain.[5] There is no evidence supporting the use of methotrexate for maintenance of remission in UC.[5] More studies are needed to determine the efficacy and safety of methotrexate maintenance therapy in patients with quiescent UC.[5]

Induction and Maintenance of Remission in Crohn's Disease

Cochrane: Oral 5-Aminosalicylic Acid for Maintenance of Surgically Induced Remission in Crohn's Disease

A June 2019 Cochrane review evaluated evidence for the safety and efficacy of 5-ASA agents for maintenance of surgically induced remission in CD.[6] Literature was searched through July 16, 2018 for RCTs that included participants with CD in remission following surgery and compared 5-ASAs to no treatment, placebo or any other active intervention with duration of at least 3 months.[6] The primary outcome was clinical relapse. Secondary outcomes included endoscopic recurrence, radiologic and surgical relapse, AEs, SAEs and withdrawal due to AEs. Fourteen RCTs (n=1867) met inclusion criteria.[6] Participants (15 to 70 years) were recruited from gastroenterology hospitals and medical clinics in Europe and North America and followed up between 3 and 72 months.[6] One study was judged to be of high quality, 6 studies were of low quality and 7 were judged to be unclear risk of bias.[6]

At 12 months, 36% of participants in the 5-ASA group experienced clinical relapse compared to 51% in the no treatment control group (RR 0.71; 95% CI 0.46 to 1.10; n=110; low certainty evidence).[6] During a follow-up period of 12 to 72 months, 36% of 5-ASA participants relapsed compared to 43% of placebo participants (RR 0.83, 95% CI 0.72 to 0.96; n=730; moderate certainty evidence).[6] At 12 months, 17% of the 4 gram/day mesalamine group relapsed compared to 26% of the 2.4 gram/day group (RR 0.65, 95% CI 0.38 to 1.13; n=206; moderate certainty evidence).[6] At 24 months, 61% of mesalamine participants relapsed compared to 67% of azathioprine participants (RR 0.90, 95% CI 0.76 to 1.07; n=347; low certainty evidence).[6] The effects of sulfasalazine compared to placebo on clinical relapse rate is uncertain.[6] After 18 to 36 months, 66% of participants treated with sulfasalazine relapsed compared to 71% in the placebo group (RR 0.88, 95% CI 0.56 to 1.38; n=298; low certainty evidence).[6]

The effect of 5-ASA drugs on safety was uncertain.[6] During 24 months follow-up, 4% of 5-ASA participants experienced AEs compared to 0% in the no treatment control group (RR 5.00, 95% CI 0.25 to 101.81; very low certainty evidence).[6] An equal proportion of 5-ASA participants (10%) and placebo (9%) groups experienced an AE during a follow-up of 3 to 72 months (RR 1.07, 95% CI 0.60 to 1.91; low certainty evidence).[6] Adverse event rates were similar in the 5-ASA and purine analogues groups.[6] However, SAEs and withdrawals due to AEs were more common in participants who received purine analogues than 5-ASA.[6] At 52 weeks to 24 months, 52% of 5-ASA participants had an AE compared to 47% of purine analogue participants (RR 1.11, 95% CI 0.97 to 1.27, low certainty evidence). Four percent of 5-ASA participants had a SAE compared to 17% of purine analogue participants (RR 0.30, 95% CI 0.11 to 0.80; very low certainty evidence). Eight percent of 5-ASA participants withdrew due to an AE compared to 19% of purine analogue participants (RR 0.48, 95% CI 0.28 to 0.83; low certainty evidence). Adverse event rates were similar in high and low dose mesalamine participants.[6] After 12 months, 2% of 4 gram/day mesalamine participants had an adverse event compared to 2% of 2.4 gram/day participants (RR 1.04, 95% CI 0.15 to 7.24; low certainty evidence).[6] None of the sulfasalazine participants had an adverse event at 18 months follow-up compared to 3% of the placebo group (RR 0.35, 95% CI 0.01 to 8.38; very low certainty evidence).[6]

In summary, 5-ASA preparations are superior to placebo for the maintenance of surgically induced clinical remission in patients with CD (moderate-quality evidence).[6] The sulfasalazine class of 5-ASA agents failed to demonstrate superiority against placebo and 5-ASAs failed to demonstrate superiority compared to no treatment (very low- and low-quality evidence).[6] The efficacy of two different doses of the same 5-ASA and the efficacy of 5-ASA compared to purine antimetabolites (azathioprine or 6-mercaptopurine) in maintaining surgically induced remission of CD remains unclear.[6] Purine analogues lead to more serious AEs and discontinuation due to AEs (low-quality evidence).[6] The 5-ASA formulations appear to be safe with no difference in the occurrence of adverse events or withdrawal when compared with placebo or no treatment (low-quality evidence).[6]

Cochrane: Azathioprine And Mercaptopurine for Maintenance of Surgically Induced Remission in Crohn's Disease

An August 2019 Cochrane review evaluated the benefits and harms of azathioprine and mercaptopurine to maintain remission in adults with CD who had undergone surgery to remove disease portions of their intestine.[7] Literature was searched through July 31, 2019 for RCTs with a duration of at least 3 months that enrolled adults and children with surgically induced remission of CD and compared azathioprine or mercaptopurine to no treatment, placebo or any other active intervention (5-ASA).[7] The primary outcome was clinical relapse. Secondary outcomes included endoscopic relapse, radiologic and surgical relapse, AEs, SAEs, withdrawal due to AEs and health-related quality of life. Ten RCTs (n=928) met inclusion criteria.[7] Most study participants were recruited less than 3 months after surgery in all except one study where participants were recruited between 6 to 24 months post-surgery.[7] One study was rated as low risk of bias, 6 studies were rated high risk of bias and 3 were rated unclear risk of bias.[7]

There was moderate-quality evidence that thiopurines are more effective for preventing clinical relapse than placebo.[7] At 12 to 36 months, 51% of azathioprine and mercaptopurine participants relapsed compared to 64% of placebo participants (RR 0.79; 95% CI 0.67 to 0.92; n=408; 3 studies; I^2 = 0%; moderate-quality evidence).[7] The quality of the evidence regarding the efficacy of azathioprine or mercaptopurine for maintaining postoperative clinical remission compared to 5-ASA compounds was low.[7] At 12 to 24 months, 64% of participants treated with thiopurines relapsed compared to 59% of 5-ASA-treated participants (RR 1.05; 95% CI 0.89 to 1.24; n=347; 4 studies; I^2 = 8%; low-quality evidence).[7]

The effect of thiopurines on AEs compared to placebo or any active treatment was uncertain, as the quality of evidence ranged from very low to low.[7] After 12 to 24 months, 14% of thiopurine-treated patients experienced an AE compared to 10% of placebo-treated patients (RR 1.36; 95% CI 0.57 to 3.27; n=168; 2 studies; I^2 = 0%; low-quality evidence).[7] The effect of thiopurines on AEs compared to 5-ASA agents was uncertain.[7] After 12 to 24 months, 41% of thiopurine-treated patients had an AE compared to 47% of 5-ASA-treated patients (RR 0.89; 95% CI 0.74 to 1.07; n=346; 4 studies; I^2 = 15%; low-quality evidence).[7] Thiopurine-treated patients were more likely than 5-ASA-treated patients to have a SAE (RR 3.39, 95% CI 1.26 to 9.13, n=311; 3 studies; I^2 = 9%; very low certainty evidence), or to withdraw due to an AE (RR 2.21, 95% CI 1.28 to 3.81; n=425; 5 studies; I^2 = 0%; low certainty evidence).[7]

In summary, moderate-quality evidence suggests that azathioprine and mercaptopurine may be superior to placebo for maintenance of surgically induced remission in participants with CD.[7] There was no clear difference in the number of clinical relapses when thiopurines were compared with 5-ASAs however this is based on low-quality evidence.[7] There was very low-quality evidence that azathioprine and mercaptopurine are more likely to result in more SAEs and withdrawals due to an AE (low-quality evidence) when compared to 5-ASA agents.[7] Further research investigating the efficacy and safety of azathioprine and mercaptopurine in comparison to other active medications in surgically induced remission of CD is warranted.[7]

Cochrane: Aminosalicylates for Induction of Remission or Response in Crohn's Disease

A July 2016 Cochrane review evaluated the efficacy of 5-ASAs compared to placebo, corticosteroids, and other aminosalicylates for the treatment of mildly to moderately active CD.[8] The primary outcome measure was a well-defined clinical endpoint of induction of remission or response to treatment. Secondary

outcomes included mean CDAI scores, AEs, SAEs and withdrawal due to AEs. Literature was searched through June 2015 to identify relevant studies.[8] Twenty studies (n=2367) met inclusion criteria.[8] Two studies were judged to be at high risk of bias due to lack of blinding.[8] Eight studies were judged to be at high risk of bias due to incomplete outcomes data (high drop-out rates) and potential selective reporting.[8] The other 10 studies were judged to be at low risk of bias.[8] Sulfasalazine was not superior to placebo for inducing remission at 17 to 26 weeks of follow-up.[8] Forty-five percent of sulfasalazine patients entered remission compared to 29% of placebo patients (RR 1.52; 95% CI 0.9 to 2.43; n= 289; 3 RCTs; p=0.08; I^2 = 41; low-quality evidence).[8] There was no difference between sulfasalazine and placebo in AEs. Seven percent of sulfasalazine patients withdrew due to an adverse event compared to 6% of placebo patients (RR 1.00, 95% CI 0.26 to 3.83; 3 RCTs; n=289; low-quality evidence).[8]

Fewer sulfasalazine patients (43%) entered remission at 17 to 18 weeks compared to 60% of corticosteroid patients (RR 0.68, 95% CI 0.51 to 0.91; 2 studies, n=260; p=0.009; moderate-quality evidence).[8] Sulfasalazine patients experienced significantly fewer AEs than corticosteroid patients (RR 0.43, 95% CI 0.22 to 0.82; 1 study, n=159; moderate-quality evidence).[8] There was no difference between sulfasalazine and corticosteroids in SAEs or withdrawal due to AEs.

Eight placebo-controlled trials evaluated the efficacy of different dosages of controlled-release mesalamine (PENTASA), delayed-release mesalamine (ASACOL) and olsalazine (DIPENTUM) for the treatment of mildly to moderately active CD.[8] In a single trial, olsalazine was less effective than placebo for remission induction (18% olsalazine vs. 49% placebo; RR 0.36, 95% CI 0.18 to 0.71; p=0.004; 91 patients; very-low quality evidence).[8] Low dose controlled-release mesalamine (1 to 2 gram/day) was not superior to placebo for induction of remission.[8] Twenty-three percent of low dose controlled-release mesalamine patients entered remission at week 16 compared to 15% of placebo patients (RR = 1.46, 95% CI 0.89 to 2.40; p=0.14; n=302; low-quality evidence).[8] There was no difference between low dose controlled-release mesalamine and placebo in the proportion of patients who had AEs (RR 1.33, 95% CI 0.91 to 1.96; 3 studies, n=342; low-quality evidence) or withdrew due to AEs (RR 1.21, 95% CI 0.75 to 1.95; 3 studies, n=342; low quality evidence).[8]

High dose controlled-release mesalamine (4 gram/day) was not superior to placebo for inducing a reduction in CDAI (mean difference [MD] -19.8 points, 95% CI -46.2 to 6.7; p=0.14; 3 studies, n=615; low-quality evidence), and was also inferior to budesonide (RR 0.56, 95% CI 0.40 to 0.78; 1 study, n=182 patients; low-quality evidence).[8] No difference between high dose delayed-release mesalamine (3 to 4.5 gram/day) and placebo was found for induction of remission (45% vs. 22%; RR 2.02, 95% CI 0.75 to 5.45; p=0.16; 1 study, n=38; very low-quality evidence), and no significant difference in efficacy was found when compared to conventional corticosteroids (57% vs. 53%; RR 1.04, 95% CI 0.79 to 1.36; 3 studies; n=178 patients, moderate-quality evidence) or budesonide (RR 0.89, 95% CI 0.76 to 1.05; p=0.17; 1 study, n=307 patients; moderate-quality evidence).[8]

In summary, in a pooled analysis of 3 RCTs, sulfasalazine was not superior to placebo for inducing remission at 17 to 26 weeks of follow-up (moderate-quality evidence).[8] Sulfasalazine is inferior to corticosteroids for the treatment of mildly to moderately active CD (moderate-quality evidence).[8] Olsalazine and low dose mesalamine (1 to 2 g/day) are not superior to placebo for induction of remission (low-quality evidence). High dose mesalamine (3.2 to 4 g/day) is not more effective than placebo for inducing response or remission (low-quality evidence).[8]

<u>Oral 5-Aminosalicylic Acid for Maintenance of Medically Induced Remission in Crohn's Disease</u>

A September 2016 Cochrane review assessed the efficacy and safety of oral 5-ASA agents for the maintenance of medically induced remission in CD.[9] Literature was searched through June 8, 2016 for RCTS of at least 6 months duration that compared oral 5-ASA agents to either placebo or sulfasalazine in patients with quiescent CD.[9] The primary outcome measure was the occurrence of relapse as defined by the primary studies. Secondary outcomes included time to relapse,

adverse events, withdrawal due to AEs and SAEs. Twelve RCTs (n=2146) that compared 5-ASA to placebo met inclusion criteria.[9] No studies that compared sulfasalazine to placebo were identified.[9] Seven studies were judged to be at low risk of bias and 3 RCTs had an unclear risk of bias.[9]

There was no statistically significant difference between 5-ASA products and placebo in relapse rates at 12 months.[9] Fifty-three percent of 5-ASA patients (dose 1.6 g to 4 gram/day) relapsed at 12 months compared to 54% of placebo patients (RR 0.98, 95% CI 0.91 to 1.07; 11 studies; n=2014; moderate-quality evidence).[9] There was no statistically significant difference in the proportion of patients who experienced an AE, withdrawal due to AEs or SAEs.[9] Thirty-four percent of 5-ASA patients had at least one AE compared to 33% of placebo patients (RR 1.05, 95% CI 0.95 to 1.17; 10 studies; n=1814).[9] Fourteen percent of 5-ASA patients withdrew due to AEs compared to 13% of placebo patients (RR 1.11, 95% CI 0.88 to 1.38; 9 studies; n=1833).[9] One percent of 5-ASA patients had a SAE compared to 0.7% of placebo patients (RR 1.43, 95% CI 0.24 to 2.83; 3 studies; n=576).[9] In conclusion, moderate-quality evidence to suggests there is no difference between oral 5-ASA preparations and placebo for the maintenance of medically induced remission in patients with CD.
After review, 11 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[54-62] or wrong study design of included trials (e.g., observational).[63,64]

New Guidelines:
High Quality Guidelines for Managing Ulcerative Colitis:
European Crohn's and Colitis Organization - Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment
Most of the evidence informing the recommendations in the 2022 ECCO guidance is from RCTs conducted in adult patients with UC.[10] The guidance stratifies disease severity into mildly to moderately active UC and moderately to severely active UC. Recommendations are presented separately for induction of remission and maintenance of remission based upon severity of disease. Recommendations and quality of evidence for oral and topical conventional therapy are summarized in **Table 2**. Supporting evidence is highlighted following the table. Evidence for conventional treatments is prioritized over evidence for biologic treatments, which is beyond the scope of this review.

Table 2. 2022 European Crohn's and Colitis Organization Recommendations for Treatment of Ulcerative Colitis[10]

Recommendation	Strength of Recommendation	Quality of Evidence
Induction of Remission in Mildly to Moderately Active Ulcerative Colitis		
5-ASA products at a dose of ≥2 g/day are recommended to induce remission in patients with mildly-to-moderately active UC.	Strong	Low
Topical (rectal) 5-ASA is recommended at a dose of ≥1 g/day for the induction of remission in active distal colitis.	Strong	Low
The use of oral 5-ASA is suggested (≥ 2 g/day) combined with topical (rectal) 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent.	Weak	Very Low
Topical steroids are recommended for the induction of remission in patients with active distal colitis.	Strong	Very Low
Treatment with topical 5-ASAs is suggested over topical steroids for induction of remission in patients with active distal UC.	Weak	Very Low
Colonic-release corticosteroids are suggested for induction of remission in patients with active mild-to-moderate UC.	Weak	Low
The use of thiopurines as monotherapy is not suggested for the induction of remission in patients with active UC.	Weak	Very Low

Maintenance of Remission in Mildly to Moderately Active Ulcerative Colitis		
The use of oral 5-ASA at a dose ≥2 g/day is recommended for maintenance of remission in UC patients.	Strong	Very Low
The use of topical 5-ASA is suggested for the maintenance of remission in patients with distal UC.	Weak	Very Low
Monotherapy with thiopurines is recommended for the maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-ASA.	Strong	Moderate
Maintenance of Remission in Moderately to Severely Active UC		
Oral prednisolone is recommended for induction of remission in non-hospitalized patients with moderately-to-severely active UC.	Strong	Very Low
Treatment with TNF inhibitors (infliximab, adalimumab, and golimumab) is recommended to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy.	Strong	Moderate
Abbreviations: 5-ASA = 5 aminosalicylic acid; g = grams; TNF = tumor necrosis factor; UC = ulcerative colitis		

Induction of Remission in Mildly to Moderately Active Ulcerative Colitis

Four trials (n=322) with a treatment duration of 3 to 8 weeks addressed whether combined oral and topical 5-ASA therapy is superior to oral monotherapy in inducing clinical remission in active UC.[10] All trials were heterogeneous in terms of patient characteristics, criteria used to define disease activity and remission, doses, and 5-ASA regimens. There was a serious inconsistency of evidence (I^2 = 71%) and a serious risk of bias, as the methods of sequence generation and allocation concealment were unclear in 3 of 4 studies.[10] The relative risk of obtaining clinical remission between combined (oral and topical) 5-ASA treatment versus oral monotherapy was 1.45 (95% CI 0.98–2.13).[10] It is difficult to compare the safety of combined versus oral 5-ASA induction treatment since only one trial addressed this outcome, with very sparse data.[10] Only 4 SAEs were detected; 3/71 patients in the combined treatment group and 1/56 patients in the oral 5-ASA plus placebo enema group experienced SAEs (RR 2.37; 95% CI 0.25 to 22.14).[10] In addition to this very serious imprecision, there was also a serious risk of bias.[10] Therefore, the quality of the data for this outcome was assessed to be very low.[10]

The use of topically administered steroids has been long established for the induction of remission in patients with proctitis and distal colitis.[10] Topically applied steroids offer the advantage over systemic steroids of a more targeted treatment with fewer systemic side effects; however, topical treatments may be poorly accepted by some patients due to the route of administration.[10] A meta-analysis of 5 RCTs that compared topical steroids with placebo showed topical steroids were superior to placebo in induction of clinical remission (pooled RR 2.12; 95% CI 1.48 to 3.06), clinical response (RR 2.18; 95% CI 1.58 to 3.01), and endoscopic response (RR 1.44; 95% CI 1.21 to 1.70].[10] Serious adverse events did not occur more frequently compared with placebo (RR 0.68; 95% CI 0.10 to 4.40).[10] The number of patients included in each study was quite low and the quality of evidence was very low.[10] This was due to indirectness and imprecision identified for the SAE outcome; a critical outcome, although other critical outcomes were judged to have high-quality evidence.[10]

The effect of treatment with topical 5-ASA at a dose ≥ 1 gram/day or topical steroids (suppositories or enemas) for induction of remission in adult patients with active distal UC has been investigated in 13 studies (n=1395) conducted over 2 to 8 weeks.[10] In a meta-analysis of these studies, topical 5-ASAs were superior for the induction of clinical remission (RR 1.36; 95% CI 1.19 to 1.56) but were not significantly more effective than topical steroids in inducing clinical response (RR 1.09; 95% CI 0.97 to 1.22).[10] In 5 studies (n=376) conducted over 2 to 4 weeks, endoscopic response was equally likely to be achieved with either topical 5-ASA or topical steroids (RR 1.08; 95% CI 0.82 to 1.44).[10] In 9 studies (n=1306) the rates of SAEs did not differ between topical 5-ASA or topical steroids (RR 1.21; 95% CI 0.47 to 3.08).[10] Overall, the quality of evidence was rated as very low.[10]

Although patients should generally be treated with a single topical agent, there is some limited evidence to suggest that combination rectal 5-ASA and rectal corticosteroid may be of benefit.[10] This may be appropriate for some patients who do not respond to initial rectal therapy.[10] It is also important to be aware of differences between preparations in terms of delivery systems and formulations, all of which may have differences in patient acceptability. It is appropriate to offer a patient a trial of an alternative preparation if they are unable to tolerate an initial choice.[10]
The effect of treatment with colonic-release corticosteroids using once-daily budesonide multi matrix (MMX) 9 mg for induction of remission in adult patients with active mild-to-moderate UC has been investigated in 3 studies (n=542) conducted over 8 weeks.[10] Colonic-release corticosteroids were superior to placebo in inducing clinical remission and clinical response (RR 2.86; 95% CI 1.62 to 5.04 and RR 1.46; 95% CI 1.11 to 1.93, respectively).[10] In 2 studies (n=510) conducted for 8 weeks, endoscopic response was more likely to be achieved with colonic-release corticosteroids in comparison with placebo (RR 1.43; 95% CI 1.10 to 1.84).[10] In all 3 studies, the rates of SAEs and of any AEs did not differ between colonic-release corticosteroids and placebo (RR 0.88; 95% CI 0.33 to 2.41 and RR:1.04; 95% CI 0.79 to 1.37, respectively).[10] The low number of SAEs resulted in a low quality of evidence, due to imprecision.[10]

A pooled analysis of data from 2 trials showed a combined clinical and endoscopic remission rate of 17.7% for budesonide MMX 9 mg/day versus 6.2% for placebo (OR 3.3; 95% CI 1.7 to 6.4).[10] Subgroup analysis of these pooled data revealed that this benefit was seen in patients with left-sided colitis, the difference between drug and placebo was not statistically significant in those with more extensive disease.[10]

Unlike other therapies, including 5-ASA, no data exist for the role of budesonide MMX as a maintenance therapy in UC.[10] This suggests that the most appropriate use of budesonide MMX may be in patients with mildly-to-moderately active disease who are not responding to or are intolerant to optimized 5-ASA therapy.[10] An RCT comparing budesonide MMX 9 mg/day with placebo, in patients with mildly-to-moderately active UC despite oral 5-ASA therapy, revealed a significant improvement in the primary endpoint of combined clinical and endoscopic remission (13% vs 7.5%; p=0.049) and histological healing in the treatment arm (27% vs 17.5%; p=0.016).[10]

Maintenance of Remission in Mildly to Moderately Active UC
Four placebo-controlled RCTs (n=232) provided data on maintenance treatment with azathioprine in patients with UC who were steroid-dependent or intolerant to 5-ASA.[10] Over one year, azathioprine was superior (56%) to placebo (35%) for the maintenance of clinical remission (RR 1.59; 95% CI 1.19 to 2.11).[10] No placebo-controlled data on endoscopic or histological remission, sustained clinical remission, or SAEs were available.[10] In contrast to current clinical trials, different disease activity indices and endpoint definitions were used; therefore, indirect comparisons with novel and potentially more potent agents are difficult.[10] Large-scale cohort studies have highlighted the apparent clinical benefit of thiopurine monotherapy.[10] Since the task force does not recommend the use of thiopurines for induction of remission, it is important that any maintenance strategy with thiopurines is planned alongside an effective induction agent.[10] No RCTs of thiopurines other than azathioprine were identified, but due to their closely related pharmacology, the recommendation was extended across the drug class.[10] Significant safety concerns do exist with the use of thiopurines.[10] This is particularly true in patients aged >65 years; use of thiopurines should be discouraged in this age group.[10] No evidence supports the use of methotrexate for the maintenance of remission in UC.[10] An RCT of methotrexate against placebo failed to demonstrate any advantage in terms of steroid-free clinical remission.[10]

Maintenance of Remission in Moderately to Severely Active UC
A previous meta-analysis identified 6 RCTs that compared systemic prednisolone with budesonide and found a significantly higher chance of induction of remission but increased steroid-related AEs with prednisolone.[10] However, none of these RCTs used a colonic-release budesonide formulation.[10] The recommendations for budesonide MMX are limited to patients with mild-to-moderately active disease, and prednisolone is limited to patients with moderately-to-severely active UC, to reflect the study populations of the RCTs identified and the likely risk-benefit profile in these different populations.[10]

It is important to note that there are no efficacy data supporting the use of corticosteroids as maintenance therapies, and very limited data on the ability of these drugs to achieve endoscopic response.[10] Additionally, longer-term corticosteroid exposure is associated with significant safety concerns.[10] Due to this, along with the availability of drugs with proven ability to maintain corticosteroid-free remission, monitoring of corticosteroid exposure in patients with UC is advised. Corticosteroid-sparing agents should be initiated for any patient showing corticosteroid-refractory disease or intolerance of or contraindication to corticosteroids. Additionally, courses of corticosteroids should be restricted to a maximum of 3 months, and therapy with a corticosteroid-sparing agent should be considered for any patient who requires more than a single course of systemic corticosteroids in a year or experiences a disease flare upon steroid tapering.[10]

American Gastroenterological Association Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis

The AGA published recommendations on the management of mild to moderate UC in 2019.[11] For this guideline, mild-moderate UC is defined as patients with fewer than 4 to 6 bowel movements per day, mild-moderate rectal bleeding, absence of constitutional symptoms, and low overall inflammatory burden.[11] The mainstay of therapy for mild-moderate UC is the 5-ASA class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA (olasalazine, balsalazide).[11] Therapeutic efficacy and safety are also similar with different 5-ASA formulations; therefore, comparability of the different commercial formulations of mesalamine at equivalent doses was assumed for purposes of this guideline.[11] For purposes of this guideline, low-dose mesalamine was defined as a total daily dose <2 grams/day, standard-dose as 2–3 grams/day, and high-dose as >3 grams/day.[11]

Mesalamine and balsalazide are generally well tolerated without significant adverse events except for the rare occurrence of interstitial nephritis.[11] Olsalazine is generally less well tolerated than either mesalamine or balsalazide, with up to a 20% risk of secretory diarrhea necessitating treatment discontinuation.[11] Although many different preparations of mesalamine are commercially available, there is little evidence to suggest differences in efficacy between them.[11] Therefore, it is not recommended to switch between mesalamine preparations in search of more effective treatment.[11] Balsalazide is the preferred diazo-bonded 5-ASA due to its better tolerability.[11] Conversely, sulfasalazine is often poorly tolerated due to side effects such as headache, nausea, diarrhea, and rash.[11] Patients often need to start at lower-dose sulfasalazine with gradual dose escalation as tolerated.[11] In addition, sulfasalazine interferes with folic acid metabolism, and patients are recommended to take folate supplementation.[11] Rare but serious cutaneous side effects, allergic reactions, hepatitis, and hematologic toxicity are also possible.[11] Because of these side effects, laboratory monitoring of complete blood counts and liver function tests is needed.[11]

Current evidence supports use of standard-dose mesalamine or diazo-bonded 5-ASAs for induction and maintenance of remission in patients with extensive mild-moderate UC.[11] Use of combined oral and rectal 5-ASA in patients with extensive disease may improve rates of induction of remission, as may escalation to high-dose oral with rectal 5-ASA in patients with suboptimal response to standard-dose therapy.[11] Those with moderate symptoms may benefit from early use of combined oral and rectal 5-ASA.[11] Patients with proctosigmoiditis or proctitis can be treated with topical mesalamines rather than oral 5-ASA.[11] Those patients with suboptimal response or intolerance to rectal mesalamine may opt to use rectal corticosteroids enemas or foams. Patients with inadequate response to optimized 5-ASA require escalation of therapy to oral prednisone or budesonide MMX.[11] Recommendation and quality of evidence are summarized in **Table 3**.

Table 3. 2019 American Gastroenterological Association Recommendations for Treatment of Ulcerative Colitis[11]

Recommendations	Strength of Recommendation	Quality of Evidence
In patients with extensive mild-moderate UC the AGA recommends using either standard dose mesalamine (2–3 g/day) or diazo-bonded 5-ASA rather than low dose mesalamine, sulfasalazine or no treatment.	Strong	Moderate
In patients with extensive mild-moderate UC, the AGA suggests adding rectal mesalamine to oral 5-ASA.	Conditional	Moderate

In patients with mild-moderate UC with suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA or with moderate disease activity, the AGA suggests using high-dose mesalamine (>3g/day) with rectal mesalamine.	Conditional	Moderate (induction) Low (maintenance)
In patients with mild-moderate UC being treated with oral mesalamine, the AGA suggests using once-daily dosing rather than multiple times per day dosing.	Conditional	Moderate
In patients with mild-moderate UC the AGA suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA, rather than budesonide MMX or controlled ileal release budesonide for induction of remission.	Conditional	Moderate
In patients with left-sided mild-moderate ulcerative proctosigmoiditis or proctitis, the AGA suggests using mesalamine enemas (or suppositories) rather than oral mesalamine.	Conditional	Very Low
In patients with mild-moderate ulcerative proctosigmoiditis who choose rectal therapy over oral therapy, the AGA suggests using mesalamine enemas rather than rectal corticosteroids.	Conditional	Moderate
Abbreviations: AGA = American Gastroenterological Association; 5-ASA = 5 aminosalicylates; g=grams; MMX = multi-matrix: UC = ulcerative colitis		

High Quality Guidelines for Managing Crohn's Disease:

European Crohn's and Colitis Organization Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

In 2019 ECCO published guidance for the medical management of adults with CD.[12] Three domains for medical treatment of CD were identified: induction therapy; maintenance therapy; and therapy of fistulizing perianal disease. ECCO recommends infliximab for the induction and maintenance of remission in complex perianal fistulae in CD (strong recommendation; low quality of evidence).[12] ECCO suggests adalimumab may be used for induction and maintenance of remission in complex perianal fistulae in Crohn's disease (weak recommendation, very low-quality evidence).[12] EECO does not suggest using thiopurine monotherapy (azathioprine, mercaptopurine) for fistula closure in patients with CD and complex perianal fistulae (weak recommendation, very low-quality evidence).[12] Recommendations and quality of evidence for induction and maintenance of remission with conventional therapy are summarized in **Table 4**. Supporting evidence is summarized following the table. Evidence for oral and topical conventional treatments is prioritized over evidence for biologic treatments, which is beyond the scope of this review.

Table 4. 2022 European Crohn's and Colitis Organization Recommendations for Use of Conventional Therapy in Treatment of Crohn's Disease[12]

Recommendations	Strength of Recommendation	Quality of Evidence
Induction of Remission		
The use of 5-ASA for induction of remission of CD is not recommended.	Weak	Moderate
Budesonide is recommended for the induction of clinical remission in patients with active, mild-to-moderate CD limited to the ileum and/or ascending colon.	Strong	Moderate
In patients with active, moderate-to-severe CD, the use of systemic corticosteroids is suggested for the induction of clinical response and remission.	Weak	Strong
The use of thiopurines as monotherapy for the induction of remission of moderate-to-severe luminal CD is not suggested.	Weak	Very Low
Maintenance of Remission		

The use of oral 5-ASA products is not recommended for maintenance of medically induced remission in patients with CD.	Strong	Low
Thiopurines are recommended for the maintenance of remission in patients with steroid-dependent CD.	Strong	Moderate
The early introduction of thiopurine therapy is not recommended in patients with newly diagnosed CD for maintaining remission.	Weak	Low
Methotrexate administered parenterally is recommended for the maintenance of remission in patients with steroid-dependent CD disease.	Weak	Moderate
It is suggested that thiopurines should be continued in CD patients in long-term remission on thiopurine maintenance therapy, as the risk of relapse is higher when the treatment is discontinued.	Weak	Low
Abbreviations: 5-ASA = 5 aminosalicylic acid; CD = Crohn's Disease		

Maintenance of Remission

Oral 5-ASA compounds have been extensively studied for the maintenance of medically induced remission of CD.[12] No statistically significant benefit has been demonstrated (RR 1.03; 95% CI 0.92 to 1.16). [12] Overall, 11 placebo-controlled trials that assessed doses between 1 and 4 gram/day were identified. [12] Treatment durations ranged from 4 months to 36 months, with most trials evaluating a 12-month duration of therapy. [12] There were no significant differences in the proportion of patients experiencing an AE or withdrawing due to AEs or SAEs (RR 1.93; 95% CI 0.18 to 21.1).[12] The safety data were very sparse (3 events) and considerably limited this conclusion.[12]

One RCT evaluated the efficacy of early use of thiopurines in CD.[12] In this study, adult patients with a recent (<8 weeks) diagnosis of uncomplicated CD were randomized to receive either azathioprine or placebo up to Week 76.[12] Only corticosteroids were allowed to treat active disease in this study population.[12] The results were not statistically significant for any of the critical outcomes evaluated.[12] After 76 weeks of treatment, clinical remission did not differ between the 2 groups (RR 1.27; 95% CI 0.94 to 1.72).[12] Thirty patients treated with azathioprine (44.1%) and 23 patients given placebo (36.5%) were in sustained corticosteroid-free remission (RR 1.21; 95% CI 0.79 to1.84).[12] The rates of relapse (defined as CDAI score >175) and corticosteroid requirements were similar between groups.[12] Serious AEs occurred in 14 patients (20.6%) in the azathioprine group and 7 (11.1%) in the placebo group (RR 1.85; 95% CI 0.8 to 4.29).[12]

Data on the use of parenterally administered MTX are derived from one double-blind, placebo-controlled RCT where patients were administered weekly intramuscular injections of 15 mg methotrexate, or placebo of identical appearance, for 40 weeks.[12] Patients with previously active CD, who had entered remission after 16 to 24 weeks of treatment with 25 mg methotrexate given intramuscularly once weekly, were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo, for 40 weeks.[12] No other treatments for CD were permitted. [12] After 40 weeks, the proportion of patients who remained in remission was higher in the methotrexate group than in the placebo group (65% vs 39 %; RR 1.67; 95% CI 1.05 to 2.67).[12] Fewer than 50% of the patients in the methotrexate group had relapsed by the end of the study.[12] There were no differences in SAEs in the methotrexate group (n=40) as compared with the placebo group (n=36) over the 40-week observational period (one patient had cervical dysplasia and the other had a viral respiratory tract infection).[12] Nausea and vomiting occurred more frequently among patients in the methotrexate group (40% vs 25% in the placebo group).[12]Although none of the symptoms was severe, one patient discontinued treatment because of these symptoms.[12] No patient had leukopenia of sufficient severity to require withholding treatment or withdrawal from the study.[12] The overall incidence of AEs was similar in both groups.[12]

Moderate-quality evidence shows budesonide is effective for the induction of remission in patients with mild-to-moderate CD, defined as a CDAI between 150 and 220, and/or presence of mild lesions at endoscopy, with ileal and/or right colon involvement.[12] Moderate-quality evidence shows 5-ASA compounds and

sulfasalazine have no therapeutic effect.[12] Although systemic steroids are effective in inducing remission in moderate-to-severe CD, they are limited by important side effects (moderate-quality evidence).[12] Additionally, long-term use of corticosteroids does not prevent disease relapse.[12] Thiopurines alone are not effective in inducing remission (very low-quality evidence).[12]

Since thiopurines have a slow onset of action (8–12 weeks) and are effective for maintaining remission in steroid-dependent CD patients they are frequently combined with steroids at the commencement of therapy (moderate-quality evidence).[12] Aminosalicylates (low-quality evidence) and steroids are not recommended to maintain remission in moderate-to-severe CD patients due to lack of efficacy and long-term risk of serious AEs (steroids).[12] The ECCO literature search and data analysis showed that immunosuppressants, such as thiopurines (moderate-quality evidence) and methotrexate (low-quality evidence) are recommended to maintain remission in steroid-dependent patients.[12] The role of adding methotrexate or thiopurines to steroids for the induction of remission is limited.[12] However, after steroids are stopped, maintenance with thiopurines or methotrexate (administered parenterally) can be an appropriate strategy (moderate-quality evidence for both drugs).[12] There is low-quality evidence supporting the continuation of thiopurines for long-term remission, as studies that directly compared long-term treatment with azathioprine, versus no treatment or placebo, did not have follow-up times greater than 18 months.[12]

AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Crohn's Disease[13]

2021 AGA guidance addresses the medical management of moderate to severe luminal and fistulizing CD.[13] There are several drug classes available for the management of moderate to severe CD, including TNF-antagonists (infliximab, adalimumab, certolizumab pegol), anti-integrin agents (natalizumab, vedolizumab), an interleukin 12/23 antagonist (ustekinumab), immunomodulators (thiopurines, methotrexate), and corticosteroids (prednisone, budesonide).[13] In general, most drugs, with the exception of corticosteroids, that are initiated for induction of remission are continued as maintenance therapy.[13]

In adult outpatients with moderate to severe CD, the AGA recommends the use of TNF-antagonists over no treatment for induction and maintenance of remission.[13] Thiopurines and methotrexate are suggested for use as combination therapies with TNF-antagonists for induction and maintenance of remission compared to TNF-antagonist monotherapy.[13] Due to lack of data, no recommendation for combination therapy with other biologics was provided.[13] Similarly, no recommendation could be made regarding withdrawal of either immunomodulators or a biologic agent over ongoing combination therapy in quiescent CD.[13] The use of natalizumab is not recommended given the side effect profile and availability of other medications to manage moderate to severe CD.[13] The use of thiopurines for induction of remission, corticosteroids for maintenance of remission and the use of mesalamine for induction or maintenance of remission are not recommended due to overall lack of efficacy.[13] Finally, for moderate to severe CD, the AGA panel suggests the early introduction of a biologic with or without an immunomodulator rather than delaying their use until after failing mesalamine and/or corticosteroids.[13] **Table 5** summarizes the AGA recommendations for conventional immunosuppressant (thiopurines, methotrexate, prednisone, and budesonide) for treatment of moderate to severe CD.

Table 5. American Gastroenterological Association Recommendations for Conventional Treatment of Moderate to Severe Crohn's Disease[13]

Recommendation	Strength of Recommendation	Quality of Evidence
In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines over no treatment for achieving remission	Conditional	Very low
In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines over no treatment for the maintenance of remission.	Conditional	Low
In adult outpatients with moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate over no treatment for the induction and maintenance of remission.	Conditional	Moderate

In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate over no treatment for the induction and maintenance of remission.	Conditional	Very low
In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission.	Strong	Moderate
In adult outpatients with moderate to severe CD, the AGA suggests the use of corticosteroids over no treatment for induction of remission.	Conditional	Moderate
In adult outpatients with moderate to severe CD, the AGA recommends against the use of corticosteroids over no treatment for maintenance of remission.	Strong	Moderate
In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-ASA or sulfasalazine over no treatment for the induction or maintenance of remission.	Strong	Moderate
Abbreviations: AGA = American Gastroenterological Association; CD = Crohn's Disease		

Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Crohn's Disease

Guidance published by the CAG in 2019 was based upon systematic search of publication databases to identify studies of medical management of pediatric CD.[14] Recommendations are summarized in **Table 6.** The 2019 CAG guidance suggests corticosteroid therapies, including budesonide, for mild to moderate pediatric CD.[14] Exclusive enteral nutrition is suggested for induction therapy and biologic TNF antagonists for induction and maintenance therapy at diagnosis or at early stages of severe disease, and for pediatric patients failed by steroid and immunosuppressant induction therapies.[14] Use of oral 5-ASA is not recommended for induction or maintenance therapy in patients with moderate disease.[14] Thiopurines are not recommended for induction therapy and corticosteroids are not recommended for maintenance therapy.[14]

Table 6. Canadian Association of Gastroenterology Recommendations for Management of Pediatric Crohn's Disease[14]

Recommendation	**Strength of Recommendation**	**Quality of Evidence**
In patients with moderate CD, the use of 5-ASAs to induce clinical remission is not recommended.	Strong	Low
In patients with moderate CD limited to the colon, the use of sulfasalazine to induce clinical remission is not recommended.	Conditional	Very Low
In patients with CD in clinical remission, sulfasalazine or 5-ASA are not recommended to maintain clinical remission.	Strong	Very Low
In patients with mild to moderate ileal and/or right colonic CD, oral controlled ileal release budesonide is suggested to induce clinical remission.	Conditional	Very Low
In patients with CD, oral controlled ileal release budesonide to maintain clinical remission is not recommended.	Strong	Very Low
In patients with moderate to severe CD, conventional corticosteroids (e.g., prednisone) are suggested to induce clinical remission.	Conditional	Very Low

In patients with mild to moderate active CD despite use of sulfasalazine, 5-ASA, oral budesonide, or exclusive enteral nutrition, oral prednisone is suggested to induce clinical remission.	Conditional	Moderate
In patients with CD of any severity, oral corticosteroids are not recommended to maintain clinical remission.	Strong	Low
In patients with CD of any severity, thiopurine monotherapy is not recommended to induce clinical remission.	Strong	Very Low
In patients with CD, parenteral is suggested methotrexate to maintain clinical remission (conditional recommendation, low-quality evidence.	Conditional	Low
Abbreviations: 5-ASA = 5-aminosalicyate; CD = Crohn's Disease		

New Formulations or Indications:

- April 2016: ENTOCORT EC (budesonide) capsules received expanded indication of mild to moderate CD involving the ileum and/or ascending colon for children 8 years and older, in addition to the long-standing indication for adults.[15] The safety and effectiveness of budesonide in pediatric patients is supported by evidence for RCTs in adults and one RCT conducted in 46 pediatric patients over 8 weeks and an additional pharmacokinetic analysis.[15] The adult dose for treatment of active mild to moderate CD is 9 mg orally once daily for up to 8 weeks.[15] In pediatric patients aged 8 to 17 years who weigh more than 25 kg, the dose is 9 mg orally once daily for 8 weeks followed by 6 mg once daily for 2 weeks.[15] Following an 8-week course of treatment for active disease, budesonide 6 mg orally once daily for maintenance of clinical remission may be continued up to 3 months.[15] Treatment beyond 3 months has not been to shown to provide substantial clinical benefit.[15]
- June 2020: LIALDA (mesalamine) delayed release tablets received expanded indication for treatment of mildly to moderately active UC in pediatric patients weighing at least 24 kg.[16] Pediatric dosing of mesalamine is weight based (2.4 grams to 4.8 grams) administered once daily as an induction dose for the first 8 weeks.[16] After 8 weeks the dose is reduced to 1.2 grams to 2.4 grams (depending on weight) once daily to maintain remission.[16] The safety and efficacy of mesalamine is supported by RCTs conducted in adults and one RCT that enrolled 105 pediatric patients aged 5 to 17 years with mild to moderate UC conducted over 34 weeks, and a pharmacokinetic analysis.[16]
- December 2021: TARPEYO (budesonide) 4 mg targeted-release capsules were approved by the FDA with an indication to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression.[17] In December 2023 the initial indication was expanded to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression.[18] The recommended dose is 16 mg once daily for 9 months, with a reduced dose of 8 mg once daily for the last 2 weeks.[17] The safety and efficacy of budesonide was evaluated in an RCT of 197 adults with biopsy-proven IgAN, eGFR ≥35 mL/min/1.73 m^2, and proteinuria who were on a stable dose of maximally tolerated renin-angiotensin system inhibitor therapy.[17] Patients with other glomerulopathies, nephrotic syndrome, or those who had been treated with systemic immunosuppressive medications were excluded.[17] Patients were randomized 1:1 to either budesonide 16 mg once daily or placebo and treated for 9 months followed by a 2-week taper of either budesonide 8 mg once daily or placebo.[17] The primary endpoint was the percentage reduction in urine protein creatine ratio (UPCR) at 9 months compared to baseline.[17] At 9 months, budesonide-treated patients had a 34% reduction in UPCR compared with a 5% reduction in UPCR in placebo-treated patients (difference: 31%; 95% CI 16 to 42; p=0.0001).[17] The most frequently reported AEs included hypertension, edema, muscle spasms, acne, dermatitis, increased weight, dyspnea, dyspepsia, and fatigue.[17]
- February 2024: EOHILA (budesonide) oral suspension received FDA approval for 12 weeks of treatment in adult and pediatric patients aged 11 years of age and older with eosinophilic esophagitis (EE).[19] This is the second FDA-approved agent for EE. Dupilumab also has approval to manage EE in adults

and pediatric patients aged 1 year and older (see **Appendix 3** for PA criteria).[42] The recommended budesonide dose is 2 mg orally twice daily for 12 weeks.[19] The safety and efficacy of budesonide was evaluated in two 12-week RCTs (n=411).[19] Eligible subjects in Study 1 and Study 2 had esophageal inflammation defined as ≥15 eosinophils/high-power field (hpf) from at least 2 levels of the esophagus at baseline following a treatment course of a proton pump inhibitor either prior to or during screening and at least 4 days of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ) over a 2-week period prior to randomization.[19] Study 1 and Study 2 evaluated efficacy endpoints of histologic remission (defined as a peak eosinophil count of ≤6/hpf across all available esophageal levels) and the absolute change from baseline in subject-reported DSQ combined score after 12 weeks of treatment.[19] At 12 weeks, 53.1% of budesonide-treated patients achieved remission compared with ~1% of placebo-treated patients in Study 1 (difference: 52.4%; 95% CI 43.3 to 59.1).[19] In study 2, 38% of budesonide-treated patients achieved remission compared with 2.4% of placebo-treated patients (difference: 35.8%; 95% CI 17.2 to 50.0) at 12 weeks.[19] The least square mean (LSM) absolute change is DSQ combined score was a -10.2 in budesonide patients and -6.5 in placebo-treated patients (difference: -3.7; 95% CI -6.8 to -0.6) in Study 1 at 12 weeks.[19] In study 2 the LSM absolute change in DSQ combined score was -14.5 for budesonide and -5.9 for placebo (difference: -8.6; 95% CI -13.7 to -3.5).[19] The most common AEs included respiratory tract infection, candidiasis, headache, gastroenteritis, throat irritation, and adrenal suppression.[19]

New FDA Safety Alerts:

Table 7. Description of new FDA Safety Alerts[65]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Mesalamine	APRISO	03/2019	Warnings and Precautions	Phenylalanine can be harmful to patients with phenylketonuria (PKU). APRISO contains phenylalanine, a component of aspartame. Each APRISO 0.375 g capsule contains 0.56 mg of phenylalanine. Before prescribing APRISO to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including APRISO.
Olsalazine	DIPENTUM	10/2020	Warnings and Precautions	Overall, approximately 17% of subjects receiving olsalazine in clinical studies reported diarrhea sometime during therapy. This diarrhea resulted in withdrawal of treatment in 6% of patients. This diarrhea appears to be dose related, although it may be difficult to distinguish from the underlying symptoms of the disease.
Mesalamine	APRISO ASACOL CANASA DELZICOL LIALDA PENTASA ROWASA	10/2020	Warnings and Precautions	*Renal Impairment* Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and renal failure have been reported in patients given mesalamine or other products that contain mesalamine or are converted to mesalamine. Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Evaluate renal

Balsalazide Olsalazine	COLAZAL DIPENTUM			function in all patients prior to initiation and periodically while on therapy with mesalamine. Evaluate the risks and benefits of using mesalamine in patients with known renal impairment or a history of renal disease or taking concomitant nephrotoxic drugs. *Acute Intolerance Syndrome* Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Symptoms include cramping, acute abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine. *Hypersensitivity* Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to mesalamine or to other compounds that contain or are converted to mesalamine. As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue PENTASA if an alternative etiology for the signs and symptoms cannot be established. *Hepatic Failure* There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered other products containing mesalamine. Evaluate the risks and benefits of using mesalamine in patients with known liver impairment. *Photosensitivity*

				Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors. *Nephrolithiasis* Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with 100% mesalamine content. Mesalamine-containing stones are radiotransparent and undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment.
Mesalamine Balsalazide Olsalazine	APRISO ASACOL CANASA DELZICOL LIALDA PENTASA ROWASA COLAZAL DIPENTUM	11/2021	Warnings and Precautions	Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in with the use of 5-ASA products. Discontinue 5-ASA at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.
Sulfasalazine	AZULFIDINE	11/2021	Warnings and Precautions	Severe, life-threatening, systemic hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking sulfasalazine. Early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, evaluate the patient immediately. Discontinue sulfasalazine if an alternative etiology for the signs or symptoms cannot be established. Other severe cutaneous adverse reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of sulfasalazine. Severe cutaneous

				adverse reactions can be serious and are sometimes fatal. Patients are at highest risk for these events early in therapy, with most events occurring within the first month of treatment. Discontinue sulfasalazine at the first appearance of signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.
Olsalazine	DIPENTUM	10/2023	Warnings and Precautions	Advise patients that urine may become discolored reddish-brown while taking olsalazine when it comes in contact with surfaces or water treated with hypochlorite-containing bleach. If discolored urine is observed, advise patients to observe their urine flow. Report to the healthcare provider only if urine is discolored on leaving the body, before contact with any surface or water (e.g., in the toilet).

Randomized Controlled Trials:
A total of 203 citations were manually reviewed from the initial literature search. After further review, 203 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).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL

mesalamine	APRISO	ORAL	CAP ER 24H	Y
mesalamine	MESALAMINE ER	ORAL	CAP ER 24H	Y
budesonide	BUDESONIDE DR	ORAL	CAPDR - ER	Y
budesonide	BUDESONIDE EC	ORAL	CAPDR - ER	Y
balsalazide disodium	BALSALAZIDE DISODIUM	ORAL	CAPSULE	Y
balsalazide disodium	COLAZAL	ORAL	CAPSULE	Y
olsalazine sodium	DIPENTUM	ORAL	CAPSULE	Y
sulfasalazine	AZULFIDINE	ORAL	TABLET	Y
sulfasalazine	SULFASALAZINE	ORAL	TABLET	Y
sulfasalazine	AZULFIDINE	ORAL	TABLET DR	Y
mesalamine	LIALDA	ORAL	TABLET DR	Y
mesalamine	MESALAMINE	ORAL	TABLET DR	Y
sulfasalazine	SULFASALAZINE	ORAL	TABLET DR	Y
sulfasalazine	SULFASALAZINE DR	ORAL	TABLET DR	Y
mesalamine	CANASA	RECTAL	SUPP.RECT	Y
mesalamine	MESALAMINE	RECTAL	SUPP.RECT	Y
mesalamine	DELZICOL	ORAL	CAP(DRTAB)	N
mesalamine	MESALAMINE DR	ORAL	CAP(DRTAB)	N
mesalamine	MESALAMINE ER	ORAL	CAPSULE ER	N
mesalamine	PENTASA	ORAL	CAPSULE ER	N
budesonide	BUDESONIDE ER	ORAL	TABDR - ER	N
budesonide	UCERIS	ORAL	TABDR - ER	N
mesalamine	MESALAMINE	ORAL	TABLET DR	N
mesalamine	MESALAMINE	RECTAL	ENEMA	N
mesalamine	ROWASA	RECTAL	ENEMA	N
mesalamine	SFROWASA	RECTAL	ENEMA	N
mesalamine w/cleansing wipes	MESALAMINE	RECTAL	ENEMA KIT	N
mesalamine w/cleansing wipes	ROWASA	RECTAL	ENEMA KIT	N
budesonide	BUDESONIDE	RECTAL	FOAM/APPL	N
budesonide	UCERIS	RECTAL	FOAM/APPL	N
budesonide	TARPEYO*	ORAL	CAPSULE DR	
budesonide	EOHILIA**	ORAL	SUSP PACKT	

* TARPEYO is FDA- approved for primary IgA nephropathy

** EOHILIA is FDA-approved for eosinophilic esophagitis

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to May Week 3 2024; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to May 23, 2024

1	exp Crohn Disease/ or exp Colitis, Ulcerative/ or exp Inflammatory Bowel Diseases/	76543
2	exp Mesalamine/	3204
3	exp Budesonide/	4537
4	balsalazide.mp.	131
5	olsalazine.mp.	137
6	exp Sulfasalazine/	2266
7	2 or 3 or 4 or 5 or 6	9694
8	1 and 7	2980
9	limit 8 to (humans and yr="2015 -Current" and (clinical trial, all or clinical trial or comparative study or consensus development conference or controlled clinical trial or equivalence trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	203

Appendix 3. Proposed Prior Authorization Criteria

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Promote use that is consistent with national clinical practice guidelines, medical evidence, and OHP-funded conditions. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators with indications for severe asthma, atopic dermatitis, or other indications (see **Table 1** below) for both pharmacy and physician-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

Covered Alternatives:

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

Table 1. FDA-Approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Eosinophilic Esophagitis	Atopic Dermatitis (AD)	Avoidance of Food Allergies	Other
Abrocitinib CIBINQO						≥12 yrs		
Benralizumab FASENRA	≥6 yrs							
Dupilumab DUPIXENT	≥6 yrs (or with oral corticosteroid dependent asthma)			≥18 yrs	≥1 yr & weighing ≥15 kg	≥6 months		PN ≥18 yrs
Mepolizumab NUCALA	≥6 yrs			≥18 yrs				HES ≥ 12 yrs EPGA ≥18 yrs
Omalizumab XOLAIR		≥6 yrs		≥18 yrs			≥ 1 yo	CSU ≥ 12 yrs
Reslizumab	≥18 yrs							

CINQAIR								
Tezepelumab TEZSPIRE			≥ 12 yrs					
Tralokinumab ADBRY						≥12 yrs		
Abbreviations: CSU = Chronic spontaneous urticaria; EPGA = Eosinophilic Granulomatosis with Polyangiitis; HES = Hyper-eosinophilic Syndrome; PN = prurigo nodularis								

Table 2. Recommended First-Line Conventional Treatments

Indication	Conventional treatment
Atopic Dermatitis	4-week trial of either one the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) in combination with a topical calcineurin inhibitor (e.g., tacrolimus) OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, or oral corticosteroids)?
Eosinophilic granulomatosis with polyangiitis (EGPA)	4-week trial of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)
Nasal polyps	Intranasal corticosteroids (2 or more courses administered for at least 12 weeks each)
Asthma	Maximally dosed inhaled corticosteroid (**Table 3**) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)
Eosinophilic esophagitis	• Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone multi-use inhaler for at least 8 weeks (use nasal inhaler and swallow contents of the spray).
Other	Documentation for conventional treatment(s) are not required

Table 3. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	Maximum Dose
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID

High Dose Corticosteroid / Long-acting Beta-agonists	Maximum Dose
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 4. Required baseline documentation disease severity

Indication	Disease severity definitions
Atopic dermatitis or prurigo nodularis	• Functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: ○ At least 10% body surface area involved, or ○ Hand, foot, face, or mucous membrane involvement
Asthma	• At least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR ○ taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR ○ at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while on conventional treatment outlined in **Table 2 and 3**
IgE-mediated food allergy	• Number of epinephrine administrations and hospital/emergency department visits (if any) in past 12 months which were caused by presumed exposure to food that triggered an allergic response
Hypereosinophilic syndrome (HES)	• Duration of disease of at least 6 months without an identifiable non-hematologic secondary cause

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved age and indication (**Table 1**)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes**: Go to #5	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. Current Age < 21 years: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the medication being prescribed by, or in consultation with, an appropriate specialist? Examples include allergist for any condition, dermatologist for atopic dermatitis, otolaryngologist for nasal polyps, or pulmonologist for asthma	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is there documentation of failure to have benefit with, or contraindication to, recommended conventional first-line treatments options (**Table 2 and 3**)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is there documentation of disease severity prior to initiation of a targeted immune modulator (**Table 4**)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the request for treatment of difficult to treat, severe asthma? Note: Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long-acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).	**Yes:** Go to #11	**No:** Go to #13
11. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.) without documentation indicating the patient is switching between treatments?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. Is the request for eosinophilic asthma, allergic asthma, or food allergies?	**Yes:** Go to #14	**No:** Go to #15
14. Is there diagnostic documentation for the requested indication? • Eosinophilic asthma: blood eosinophil count ≥150 cells/μL OR fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months • Allergic IgE-mediated asthma: positive skin test OR in vitro reactivity to perennial allergen • Food allergy: IgE-mediated food allergy with skin testing to confirm allergy OR in vitro reactivity to perennial allergen	**Yes:** Approve for up to 12 months. Document test and result:_____	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the request for a JAK inhibitor (e.g., abrocitinib)?	**Yes:** Go to #16	**No:** Go to #17

Approval Criteria		
16. Has the patient failed to have benefit with or have intolerance or contraindication to alternative targeted immumodulatory therapy?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
17. Duration of approval based on indication:	Asthma, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and chronic spontaneous urticaria: 12 months All other conditions: requested duration or 6 months, whichever is less	

Renewal Criteria		
1. Is the request to renew therapy for inflammatory skin disease?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with targeted immune modulator therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for asthma?	**Yes:** Go to #4	**No:** Go to #6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
5. Has the number of emergency department (ED) visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request to renew therapy for another FDA approved indication?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* *http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed May 2, 2023.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

P&T Review: *10/24; 8/24 (DM); 6/23 (DM); 10/22 (DM) 6/22 (DM); 8/21 (DM); 10/20 (KS),7/19; 7/18; 7/16*
Implementation: *7/1/23; 1/1/23; 7/1/22; 1/1/22*

Budesonide Oral Suspension

Goal(s):
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of cost-effective products.

Length of Authorization:
- Up to 12 weeks

Requires PA:
- Budesonide (Eohilia™) oral suspension for pharmacy claims.

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved age and indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is there documentation of failure to have benefit with, or contraindication to: • Proton pump inhibitor therapy for at least 8 weeks AND • Corticosteroid therapy with local administration of fluticasone nasal inhaler for at least 8 weeks (use inhaler and swallow contents of the spray).	**Yes:** Approve for 12 weeks of therapy for one course of treatment. Note: Budesonide oral suspension has not been shown to be safe and effective for the treatment of erosive esophagitis for longer than 12 weeks.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *10/24 (DM)*
Implementation: *12/1/2024*