Therapeutic Class Overview
Inflammatory Bowel Disease Agents

INTRODUCTION

- Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding, fatigue, and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic, and lifestyle factors *(Bernstein et al 2015, Peppercorn 2018[a], Peppercorn, 2018[c]).*
- Complications of IBD include hemorrhage, rectal fissures, fistulas, peri-rectal and intra-abdominal abscesses, and colon cancer. Possible extra-intestinal complications include hepatobiliary complications, anemia, arthritis and arthralgias, uveitis, skin lesions, and mood and anxiety disorders *(Bernstein et al 2015).*
- Ulcerative colitis (UC) and Crohn's disease (CD) are 2 forms of IBD that differ in pathophysiology and presentation; as a result of these differences, the approach to the treatment of each condition often differs *(Peppercorn 2018[a]).*
- UC is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus *(Kornbluth et al 2010, Peppercorn 2018[c]).*
- CD can involve any part of the gastrointestinal tract and is characterized by transmural inflammation and "skip areas." Transmural inflammation may lead to fibrosis, strictures, sinus tracts, and fistulae *(Peppercorn 2018[b]).*
- The immune system is known to play a critical role in the underlying pathogenesis of IBD. It is suggested that abnormal responses of both innate and adaptive immunity mechanisms induce aberrant intestinal tract inflammation in IBD patients *(Geremia et al 2014).*
- Precise incidence and prevalence of CD and UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the United States (U.S.) incidence rate of UC varies between 2.2 to 14.3 per 100,000 person-years and the incidence of CD varies from 3.1 to 14.6 per 100,000 person-years. As many as 3 million persons in the U.S. suffer from IBD *(Centers for Disease Control and Prevention [CDC] 2015, CDC 2018).*
- Some risk factors for IBD include age, gender, race, ethnicity, genetics, smoking status, and dietary considerations (*Peppercorn 2018[a]*).
  - The typical age of onset of IBD is between 15 and 40 years, while a second peak between ages 50 and 80 years has been noted.
  - Caucasians tend to have a higher incidence of IBD compared to Hispanic and Black populations. Additionally, ethnic and racial differences may be related to environmental and lifestyle factors as well as underlying genetic differences.
  - Genetic susceptibility to IBD is not completely understood; however, it is estimated that nearly 10 to 25% of individuals afflicted with IBD have a first-degree relative with IBD.
  - Smoking status affects CD and UC differently, being associated with an increased risk with CD and a decreased risk with UC.
  - Dietary factors have been associated as risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, processed, fried, and sugar-laden foods are associated with an increased risk of developing CD and possibly UC.
- The goals for the treatment of IBD include resolution of intestinal inflammation and healing of the mucosa; elimination of symptoms while minimizing side effects; maintenance of corticosteroid-free remission; prevention of complications, hospitalization, and surgery; and maintenance of good nutritional status *(Bernstein et al 2015).*
- Current pharmacotherapy for UC includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, Remicade [infliximab], Humira [adalimumab]) *(Micromedex 2019; Bernstein et al 2015).*
  - Choice of therapy is based on several factors, including disease severity, anatomic extent, and response to prior therapies *(Kornbluth et al 2010).*
  - Inflammation that is distal is limited to below the descending colon and within reach of topical therapy. Inflammation that extends proximal to the descending colon requires systemic medication *(Kornbluth et al 2010).*

- Although the specific Food and Drug Administration (FDA)-approved indications of the oral 5-ASA derivative preparations vary, these agents are used in the treatment and maintenance of remission of UC. The oral 5-ASA derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine (*Kornbluth et al 2010)*. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine (*Prescribing information: Colazal 2016, Dipentum 2014)*. The 5-ASA derivatives have not shown differences in safety or efficacy; therefore, the choice of treatment agent should be based on indication, location of the disease, expected patient compliance with the regimen, patient preference, and availability of the drug *(Cheifetz 2018)*.
- Budesonide (Uceris) is available in an extended release tablet which delays the release of budesonide until it reaches the site of action (*Prescribing information: Uceris tablet 2018*). Budesonide is also available as a rectal foam (Uceris). Budesonide extended-release capsules (Entocort EC) are approved for the treatment and maintenance of remission of CD. (*Prescribing information: Entocort EC 2019*).
- Sulfasalazine (Azulfidine EN-tabs) is also FDA-approved for the treatment of rheumatoid arthritis nonresponsive to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDS) and for pediatric polyarticular-course juvenile rheumatoid arthritis (*Prescribing information: Azulfidine EN-Tabs 2016)*.
- Other injectable biologic response modifiers known as monoclonal antibodies (MABs) are also approved to treat UC and/or CD including the tumor necrosis factor (TNF) inhibitors (eg, Cimzia [certolizumab pegol], Humira [adalimumab], Amjevita [adalimumab-atto], Hyrimoz (adalimumab-adaz), Cyltezo [adalimumab-adbm], Simponi [golimumab], Inflectra [infliximab-dyyb], Ixifi [infliximab-qbtx], Renflexis [infliximab-abda] and Remicade [infliximab]). In 2014, the alpha-4 beta-7 (α4β7) integrin receptor antagonist, Entyvio (vedolizumab) was approved for treatment of moderately to severely active UC and CD in adult patients who have had an inadequate response with, lost response to, or were intolerant to a TNF inhibitor or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. In 2016, Stelara [ustekinumab] was approved for the treatment of moderate to severely active CD in adult patients who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a TNF blocker or in those who have failed or were intolerant to treatment with 1 or more TNF blockers. In 2018, Xeljanz [tofacitinib] was approved for the treatment of moderately to severely active UC, as an orally administered targeted agent (*Micromedex 2019, Drugs@FDA 2019).* Additional injectable, humanized MABs are being studied for the treatment of various forms of IBD. These are reviewed in the Immunomodulators Class.
- The scope of this review will focus upon the oral and topical agents outlined in Table 1 for their respective FDA-approved, gastrointestinal-related indications.
- Medispan Therapeutic Class: Inflammatory Bowel Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Apriso (mesalamine) ER capsule	-
Asacol HD (mesalamine) DR tablet	✔
Azulfidine (sulfasalazine) tablet	✔
Azulfidine EN-tabs (sulfasalazine) DR tablet	✔
Canasa (mesalamine) rectal suppository	✔
Colazal (balsalazide) capsule	✔
Delzicol (mesalamine) DR capsule	-
Dipentum (olsalazine) capsule	-
Entocort EC (budesonide) DR capsule	✔
Lialda (mesalamine) DR tablet	✔
Pentasa (mesalamine) CR capsule	-
Rowasa (mesalamine) rectal enema suspension	✔
sfRowasa (mesalamine) rectal enema suspension (sulfite-free)	-
Uceris (budesonide) ER tablet	✔
Uceris (budesonide) rectal foam	-

CR=controlled release, DR=delayed release, EC=enteric coated, ER=extended release
Asacol (mesalamine) by Warner Chilcott was discontinued by the manufacturer in the spring of 2013 due to a business decision. A generic is not currently available.
Giazo (balsalazide) 1.1 gm tablet was discontinued in 8/2018. A generic is not currently available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients ≥ 8 years of age		✔ (Entocort EC)			
Treatment of mildly to moderately active UC in patients ≥ 5 years of age	✔ (Colazal)†	-	✔ (Delzicol)	-	-
Treatment of moderately active UC in adults	-	-	✔ (Asacol HD)*	-	-
Induction of remission in adults with active, mild to moderate UC	-	✔ (Uceris tablet)	✔ (Lialda)	-	-
Induction of remission in adults with active mild to moderate distal UC extending up to 40 cm from the anal verge	-	✔ (Uceris rectal foam)	-	-	-
Maintenance of remission of mild to moderate Crohn's disease involving the ileum and/or ascending colon for up to 3 months in adults		✔ (Entocort EC) ***			
Maintenance of remission of UC in adults	-	-	✔ (Apriso; Delzicol; Lialda)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	-	✔	-
Induction of remission and for the treatment of patients with mildly to moderately active UC	-	-	✔ (Pentasa)	-	-
Treatment of mildly to moderately active ulcerative proctitis	-	-	✔ (Canasa)	-	-
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	-	✔ (Rowasa; sfRowasa)	-	-
Treatment of mild to moderate UC, and as adjunctive therapy in severe UC	-	-	-	-	✔ (Azulfidine; Azulfidine EN-tabs**)
Prolongation of the remission period between acute attacks of UC	-	-	-	-	✔ (Azulfidine; Azulfidine EN-tabs**)
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (eg, an insufficient therapeutic response to, or intolerance of, an	-	-	-	-	✔ (Azulfidine EN-tabs)

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
adequate trial of full doses of 1 or more NSAIDs)					
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs	-	-	-	-	✔ (Azulfidine EN-tabs)

*Safety and effectiveness of Asacol HD beyond 6 weeks have not been established.
**Azulfidine EN-tabs are specifically indicated in patients with UC who cannot tolerate sulfasalazine tablets due to gastrointestinal intolerance when the gastrointestinal intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites.
***Taper to complete cessation after 3 months; continued treatment for more than 3 months has not been shown to provide substantial clinical benefit
†Safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

(Prescribing information: Apriso 2018, Asacol HD 2018, Azulfidine 2016, Azulfidine EN-Tabs 2016, Canasa 2017, Colazal 2016, Delzicol 2019, Dipentum 2014, Entocort EC 2019, Lialda 2018, Pentasa 2018, Rowasa 2017, sfRowasa 2017, Uceris tablet 2018, Uceris rectal foam 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Oral therapy

- Multiple systematic reviews have been published evaluating randomized clinical trials of mesalamine products for UC. No significant differences in safety or efficacy between the mesalamine products have been found in the systematic reviews.
  - In a 2013 Cochrane review of 17 randomized clinical trials (N = 2925), the efficacy and safety of oral mesalamine products used for induction and maintenance of remission of UC were evaluated. The primary outcomes were failure to induce global or clinical remission or improvement, and failure to maintain global or clinical remission (relapse). Products included balsalazide, olsalazine, Pentasa, Asacol, Lialda, and 3 mesalamine products which are not available in the U.S. For the failure to induce global or clinical remission in mild to moderately active UC endpoint, there was no significant difference between the 5-ASA formulations (balsalazide, Pentasa, olsalazine, Lialda, mesalamine, and 5-ASA micropellets) and the comparator group (Asacol and 2 mesalamine formulations) (11 studies, N = 1968, 50% vs 52%, pooled relative risk [RR] 0.94, 95% confidence interval [CI], 0.86 to 1.02, $I^2 = 0\%$, p = 0.11). For failure to induce global or clinical remission or improvement, a total of 8 studies with 1647 patients were evaluated, and results demonstrated that there was no difference between the 5-ASA products (balsalazide, Pentasa, olsalazine, Lialda, and 5-ASA micropellets) and the 5-ASA comparators (Asacol, 2 mesalamine formulations, and Pentasa) (30% vs 35%, pooled RR 0.89, 95% CI, 0.77 to 1.01, $I^2 = 0\%$, p = 0.08) using a fixed-effects model. Note that Pentasa was on both sides of the comparison for this endpoint. For the failure to maintain global or clinical or endoscopic remission at 12 months, there was no difference between the 5-ASA formulations (balsalazide, Pentasa, and olsalazine) and the comparators (Asacol, mesalamine) in 5 studies (N = 457) (38% vs 37%, pooled RR 1.01, 95% CI, 0.80 to 1.28, $I^2 = 39\%$, p = 0.95). The incidences of adverse events between the various formulations were not significantly different. Risk of bias was low for most study factors; however, 1 study was single-blind, and 3 were open-label. There were numerous products in this systematic review which are not currently available in the U.S. *(Feagan et al 2013).*
  - A 2016 Cochrane review of 53 studies with 8548 patients with UC evaluated the oral 5-ASA preparations and sulfasalazine for the induction of active UC remission. The newer 5-ASA derivatives were “superior” to placebo with 71% of 5-ASA patients failing to enter clinical remission compared to 83% for placebo (11 studies; N = 2387; RR 0.86, 95% CI, 0.82 to 0.89). No statistically significant differences in efficacy between 5-ASA and sulfasalazine were observed, with 54% of 5-ASA-treated patients and 58% of sulfasalazine-treated patients failing to enter remission (8 studies; N = 526; RR 0.90, 95% CI, 0.77 to 1.04). Adherence did not appear to be enhanced by once daily dosing in the clinical trials; however, it is not known if once daily dosing would improve adherence in the community setting. Failure to enter clinical remission rates were 45% for once daily vs 48% for conventional dosing regimens (4 studies;

N = 944; RR 0.94, 95% CI, 0.83 to 1.07). No significant differences among the 5-ASA products for safety and efficacy were found *(Wang et al 2016[a]).*

- In a 2016 Cochrane review of 41 studies with 8928 patients, all 5-ASA formulations were "superior" to placebo for maintenance of clinical or endoscopic remission of UC. Relapse rates were 41% for 5-ASA-treated patients and 58% for placebo-treated patients (7 studies; N = 1298; RR 0.69; 95% CI, 0.62 to 0.77). Sulfasalazine was found to have a statistically significant benefit over 5-ASA in the maintenance of UC when looking at all trials at study endpoint (12 studies; N = 1655; RR 1.14, 95% CI, 1.03 to 1.27); however, when only trials of 12 months or longer were evaluated, there was no longer a difference between sulfasalazine and 5-ASA (8 studies; N = not reported; RR 1.10, 95% CI, 0.98 to1.23). No significant difference in efficacy was demonstrated between once daily and conventional dosing regimens; 29% of once daily-treated patients relapsed over 12 months vs 31% of conventionally dosed patients (8 studies; N = 3127; RR 0.91, 95% CI, 0.82 to 1.01). No significant difference in efficacy was found when comparing the various 5-ASA formulations. Relapse rate was 44% in the 5-ASA group vs 41% in the 5-ASA comparator group (6 studies; N = 707; RR 1.08, 95% CI, 0.91 to 1.28). No statistically significant differences were found for the incidence of adverse events between 5-ASA and placebo, 5-ASA and sulfasalazine, once daily and conventionally dosed 5-ASA, 5-ASA and comparator 5-ASA formulations, and 5-ASA dose ranging studies *(Wang et al 2016[b]).*
- A network meta-analysis evaluated the comparative efficacy and tolerability of agents used to treat mild to moderate UC. The analysis included 75 trials (12,215 patients) that evaluated either sulfasalazine, diazo-bonded 5-ASA, mesalamine, or budesonide, alone or in combination with rectal 5-ASA therapy. Agents were ranked using surface under the cumulative ranking curve (SUCRA) probabilities. For the induction of remission, combined oral and rectal 5-ASAs (SUCRA, 0.99) and high-dose mesalamine (> 3 g/day; SUCRA, 0.82) were the highest ranked therapies; both were also found to be superior to standard-dose mesalamine. For the maintenance of remission, all therapies were found to be superior to placebo, but high-dose mesalamine was not superior to standard-dose mesalamine (*Nguyen et al 2018*).
- Another systematic review evaluated once daily oral mesalamine compared to conventional dosing regimens of oral mesalamine for induction and maintenance of remission of UC in 11 studies with 4070 patients. Of the 11 studies, 5 studies were single-blind, and 1 study was performed in an open-label manner. Products assessed were Lialda, Asacol, Pentasa, and Salofalk (mesalazine - not available in the U.S.). Failure to induce global or clinical remission was not different between once daily and conventional dosing of mesalamine (3 studies, N = 738; pooled RR 0.95, 95% CI, 0.82 to 1.10; I^2 = 0%). No difference was observed between dosing regimens in failure to maintain global or clinical remission at 12 months (5 studies, N = 1394; pooled RR 0.92, 95% CI, 0.83 to 1.03, I^2 = 40.9%). Rates of medication adherence or adverse events between once daily and conventional dosing regimens of mesalamine were not significantly different. The authors noted that adherence rates in clinical trials may be higher than real world usage *(Feagan and MacDonald 2012).*
- A meta-analysis of 10 studies that evaluated mesalamine once daily vs multiple daily dosing regimens in 3410 patients with quiescent UC was conducted to determine the efficacy in preventing a relapse. The intention to treat analysis found that mesalamine once daily (26.3%) was as effective as multiple daily doses (26.5%) (8 studies, RR 1.00, 95% CI, 0.89 to 1.12, I^2 = 41%, p = 0.105). An analysis of the efficacy of once daily vs multiple daily dosing of mesalamine for inducing remission in active UC found that remission was not observed in 29.8% of patients on once daily mesalamine and 37.8% of patients receiving multiple daily doses. The risk of failure to achieve remission was higher with multiple daily doses (2 studies, RR 0.80; 95% CI, 0.64 to 0.99, I^2 = 21.6%, p = 0.259). When evaluating the same outcome on a per-protocol analysis, there was no significant difference between the 2 groups. No significant differences in adverse events were observed between the 2 groups *(Tong et al 2012).*
- In another 2012 meta-analysis, 9 of 10 studies included in the Tong et al analysis were evaluated by another group *(Zhu et al 2012).* There were no significant differences for once daily compared to more frequent dosing (twice or 3 times daily) of mesalamine for UC for the maintenance of clinical remission, endoscopic remission, maintenance of combined clinical and endoscopic remission, and the overall incidence of adverse events.

- A Cochrane review evaluated oral budesonide for induction of remission in UC. A total of 6 studies (N = 1808) were evaluated. Budesonide multi-matrix (MMX) (Uceris) 9 mg was superior to placebo for inducing remission at 8 weeks (15% vs 7%, respectively; 3 studies, N = 900; RR 2.25, 95% CI, 1.50 to 3.39; moderate quality of evidence). An analysis of 2 studies with budesonide MMX 6 mg showed that it was not superior to placebo for induction of remission (11% vs 6%, respectively; 2 studies, N = 440; RR 1.80, 95% CI, 0.94 to 3.42; low quality of evidence). Budesonide (Entocort EC) was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks (1 study, N = 343; RR 0.72, 95% CI 0.57 to 0.91; moderate quality of evidence). However, another study found no difference in remission rates between budesonide MMX 9 mg and mesalamine (1 study; N = 247; RR 1.48, 95% CI, 0.81 to 2.71; low quality of evidence). In a comparison of the 2 budesonide formulations, there was no difference in remission rates between

budesonide MMX 9 mg and budesonide 9 mg (1 study, N = 212; RR 1.38, 95%CI, 0.72 to 2.65; low quality of evidence) *(Sherlock et al, 2015).*

- Two additional Cochrane reviews have evaluated oral budesonide for induction and maintenance of remission in CD.
  - For induction of remission, budesonide was found to be superior to placebo at 8 weeks (47% vs 22%, respectively; 3 studies, N = 379; RR 1.93, 95% CI, 1.37 to 2.73; moderate quality of evidence). Budesonide was found to be significantly less effective than conventional steroids (52% vs 61%, respectively; 8 studies, N = 750; RR 0.85, 95% CI, 0.75 to 0.97; moderate quality of evidence), but treatment with budesonide resulted in significantly fewer adverse events (RR 0.64, 95% CI, 0.54 to 0.76) (*Rezaie et al, 2015*).
  - For maintenance of remission, budesonide 6 mg daily was not found to be more effective than placebo at 3, 6, or 12 months. The authors concluded that budesonide is not effective for maintenance of remission in CD, particularly when used longer than 3 months following the induction of remission (*Kuenzig et al, 2014*).

Topical therapy

- According to a meta-analysis comparing rectal 5-ASA therapy to either placebo or other active agents for the treatment of distal disease, rectal 5-ASA was superior to placebo and rectal corticosteroids. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement *(Marshall et al 2010).* A 2012 smaller meta-analysis found that rectal 5-ASA therapy was superior to placebo and similar to oral 5-ASA on rates of symptomatic remission and endoscopic remission. No dose response relationship for 5-ASA enemas or other rectal dosage forms has been observed *(Marshall et al 2012).*
- A meta-analysis found greater efficacy with topical mesalamine than placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat (NNT) of 3. Time to relapse was longer with topical mesalamine in the 2 trials, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy *(Ford et al 2012[b]).*
- Budesonide rectal foam was compared to placebo in 2 randomized, Phase 3 trials in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. Compared to placebo, a significantly greater proportion of patients receiving budesonide rectal foam experienced remission, resolution of rectal bleeding, and endoscopic improvement at week 6 ($p < 0.05$ for all comparisons in both trials) *(Sandborn et al 2015).* Additionally, in a randomized, Phase 3 trial in patients with mild to moderate UC with distal active inflammation, significantly more patients who received budesonide rectal foam experienced clinical remission and complete mucosal healing of distal lesions compared to placebo ($p = 0.0035$ and $p = 0.0003$, respectively) *(Naganuma et al 2017)*.

Oral vs. topical mesalamine

- A meta-analysis found combined oral and topical 5-ASA therapy to be superior to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Additionally, intermittent topical 5-ASA therapy was reported to be superior to oral 5-ASA therapy for preventing relapse of quiescent UC *(Ford et al 2012[a]).*

CLINICAL GUIDELINES

- The 2010 Ulcerative Colitis Practice Guidelines in Adults from the American College of Gastroenterology (ACG) recommend oral mesalamine but do not differentiate between the different oral formulations available; a blanket recommendation for mesalamine is provided. All aminosalicylates are superior to placebo and equivalent to sulfasalazine in acute therapy of UC *(Kornbluth et al 2010).* A guideline update is underway *(ACG 2019).*
  - For the management of mild to moderate distal colitis, oral aminosalicylates, topical mesalamine, or topical corticosteroids are recommended (Evidence A [defined as High level of evidence; further research is very unlikely to change our confidence in the estimate of effect). Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical agents is “superior” to each agent used alone (Evidence A). Oral therapies effective for achieving and maintaining remission include balsalazide, mesalamine, olsalazine, and sulfasalazine. For the maintenance of remission in distal disease, mesalamine suppositories are effective for maintenance of remission in patients with proctitis, and mesalamine enemas are effective in patients with distal colitis (Evidence A). Balsalazide, mesalamine, and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone (Evidence A). Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission (Evidence A).
  - For the management of active mild to moderate extensive colitis, oral sulfasalazine or oral aminosalicylates in doses up to 4.8 g per day of the active 5-ASA moiety are considered first-line (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates or patients who require rapid improvement (Evidence B [defined as Moderate level of evidence; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.]). For patients refractory to oral corticosteroids, 6-MP or azathioprine can be used for patients who are acutely ill, requiring intravenous therapy (Evidence A). Infliximab is effective in patients who are steroid refractory or steroid-dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. For maintenance of remission for mild to moderate extensive colitis,

balsalazide, mesalamine, olsalazine, and sulfasalazine are effective in reducing the number of relapses (Evidence A). Azathioprine or 6-MP can be used for steroid sparing in steroid-dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates (Evidence A). Infliximab effectively maintains remission in patients who responded to the infliximab induction regimen (Evidence A).
  - For the management of severe colitis in a patient who is refractory to maximum oral treatment with aminosalicylates, oral prednisone, and topical medications, infliximab is a treatment option if urgent hospitalization is not required (Evidence A). Patients who show signs of toxicity should be hospitalized to receive intravenous steroids. Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown (Evidence A).
- The 2018 guidelines on management of Crohn's Disease in Adults from the ACG recommend controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD (strong recommendation, low level of evidence). They do not recommend use of budesonide beyond 4 months (strong recommendation, moderate level of evidence). The guideline also recommends against the use of oral mesalamine to treat patients with active CD, since it has not consistently been shown effective for inducing remission and achieving mucosal healing when compared to placebo (strong recommendation, moderate level of evidence). Sulfasalazine is recommended for symptoms of mild to moderate colonic CD (conditional recommendation, low level of evidence) (*Lichtenstein et al 2018*).
- The World Gastroenterology Organization Global Guidelines state that 5-ASA products are useful for treating both colitis flare-ups and maintenance of remission. A combination of oral with topical 5-ASA products is more effective than oral agents alone for induction of remission of mild to moderate UC. Rectal 5-ASA products are more beneficial than rectal corticosteroids in UC. Limited evidence exists for 5-ASA products in CD; these products are mainly used in patients who cannot tolerate corticosteroids. Corticosteroids provide rapid relief of symptoms by suppressing inflammation and should be used to induce remission; they have no role in maintenance of remission and side effects limit duration of use. Budesonide may have fewer adverse events than other corticosteroid options *(Bernstein et al 2015).*
- The American Gastroenterological Association (AGA) guideline on the management of mild to moderate UC recommends standard-dose oral mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease, rather than low-dose mesalamine, sulfasalazine, or no treatment (strong recommendation, moderate evidence). The guideline also suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA over budesonide preparations for induction of remission (conditional recommendation, low evidence) (*Ko et al 2019*).
  - For management of extensive or left-sided disease, rectal mesalamine can be added to oral 5-ASA (conditional recommendation, moderate evidence). For management of left-sided ulcerative proctosigmoiditis or proctitis, mesalamine enemas or suppositories are suggested over oral mesalamine (conditional recommendation, very low evidence). Further, in patients with ulcerative proctosigmoiditis, mesalamine enemas are suggested over rectal corticosteroids (conditional recommendation, moderate evidence).
  - For patients who have a suboptimal response to first-line treatment for mild to moderate UC, high-dose mesalamine (> 3 g/day) with rectal mesalamine is suggested (conditional recommendation, moderate evidence for induction, low evidence for maintenance).
- The ACG recently released a clinical guideline addressing preventive care in IBD. According to published data, patients with IBD do not receive preventive care services at the same rate as general medical patients. Increased coordination between gastroenterology and primary care providers is recommended, as well as proper age-appropriate immunization, cervical and skin cancer screenings, depression and anxiety screening, and smoking cessation counseling for patients with CD *(Farraye et al 2017).*
- The AGA pregnancy care pathway for inflammatory bowel disease recommends that aminosalicylates may be continued during pregnancy, delivery, and during the postpartum period. For maintenance therapy in pregnancy, monotherapy is preferred. The pathway notes that Azulfidine EN-tabs contains phthalates, which may be better to avoid in pregnancy, and all mesalamine preparations are phthalate-free. Both mesalamine and sulfasalazine are compatible with breastfeeding, though mesalamine is preferred (*Mahadevan et al 2019*).

SAFETY SUMMARY

- Contraindications include hypersensitivity to salicylates or any component for the drugs in this class. Sulfasalazine is contraindicated in patients with intestinal or urinary obstruction or in patients with porphyria, as sulfonamides may precipitate an acute attack.
- Warnings include mesalamine acute intolerance syndrome, exacerbations of colitis, and caution using drugs in this class in patients with hepatic or renal impairment. Mesalamine products (Lialda, Pentasa, and Canasa) and sulfasalazine

products (Azulfidine and Azulfidine EN-tabs) may interfere with laboratory tests for normetanephrine. Rectal mesalamine may cause oligospermia and pancolitis.

- Due to the potential for severe blood dyscrasias, complete blood counts, including differential white cell count, and liver function tests should be performed before starting sulfasalazine therapy (Azulfidine and Azulfidine EN-tabs) and every second week during the first 3 months of therapy; tests should be repeated once monthly for 3 months, then once every 3 months, and as clinically indicated.
- Budesonide may cause hypercorticism, adrenal axis suppression, and increased risk of infection.
- Concurrent use of NSAIDs with mesalamine products may increase the risk of nephrotoxicity; use with caution.
- Oral mesalamine and Canasa should not be used with 6-mercaptopurine and azathioprine due to decreased thiopurine metabolism; an increased risk of myelosuppression may result.
- In general, the inflammatory bowel agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Balsalazide	Capsule (Colazal) 750 mg	Oral	Capsule (Colazal): 3 times daily	Capsule (Colazal): approved for use in children 5 to 17 years old
Budesonide	Delayed-release capsule (Entocort EC) 3 mg Extended-release tablet (Uceris) 9 mg Rectal foam (Uceris) 2 mg/actuation	Oral, Rectal	Delayed-release capsule: once daily Extended-release tablet: once daily Rectal foam: once to twice daily	Delayed-release capsule (Entocort EC) is used to treat active CD (children ≥ 8 years of age); Uceris is used to treat UC Patients with moderate to severe hepatic impairment should be monitored for signs and symptoms of hypercorticism
Mesalamine	Controlled-release capsule (Pentasa) 250 mg, 500 mg Delayed-release capsule (Delzicol) 400 mg Delayed-release tablet 800 mg (Asacol HD), 1.2 g (Lialda) Extended-release capsule (Apriso) 0.375 g Rectal suppository (Canasa) 1000 mg Rectal enema (Rowasa, sfRowasa) 4 g/60 mL	Oral, Rectal	Controlled-release capsule (Pentasa): 4 times daily Delayed-release capsule (Delzicol): twice to 4 times daily Delayed-release tablet (Asacol HD): 3 times daily Delayed-release tablet (Lialda): once daily Extended-release capsules (Apriso): once daily Rectal suppository (Canasa): once daily at bedtime Rectal enema (Rowasa; sfRowasa): once daily at bedtime	Delayed-release capsule (Delzicol): approved for use in children ≥ 5 years of age Complete blood counts should be periodically monitored in elderly patients. Renal function should be evaluated prior to initiation of most mesalamine products; use with caution in patients with a history of or known renal dysfunction. Two Delzicol 400 mg capsules have not been shown to be interchangeable or substitutable with one Asacol HD tablet.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Olsalazine (Dipentum)	Capsule 250 mg	Oral	Twice daily	
Sulfasalazine	Tablet (Azulfidine) 500 mg Delayed-release tablet (Azulfidine EN-tabs) 500 mg	Oral	Tablet and delayed-release tablet: twice to 4 times daily	Sulfasalazine products may cause an orange-yellow discoloration of the urine or skin. Safety and effectiveness for UC in patients < 2 years of age have not been established. FDA-approved for rheumatoid arthritis in adults and juvenile rheumatoid arthritis for children ≥ 6 years of age. (Azulfidine EN-tabs only)

See the current prescribing information for full details

CONCLUSION

- Treatment goals of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations, and maintain remission from acute inflammation.
- For induction of remission of UC, no differences in efficacy or safety among the oral 5-ASA formulations have been identified *(Wang et al 2016[a]).* Oral 5-ASA is similarly effective to sulfasalazine for induction of UC remission *(Kornbluth et al 2010)*.
- No overall differences in efficacy or safety among the oral 5-ASA formulations have been observed for the maintenance of UC remission *(Wang et al 2016[b]).* Once daily dosing and traditional dosing of oral 5-ASA regimens were similarly effective for maintenance of UC remission *(Feagan and MacDonald 2012, Feagan et al 2013).*
- Topical rectal therapies are the formulations of choice for distal disease and have been shown to be more effective than oral sulfasalazine therapy. In a meta-analysis, rectal 5-ASA therapy was shown to be superior to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not superior to oral 5-ASA for symptomatic improvement or remission rates *(Marshall et al 2010).* For maintenance of symptomatic and endoscopic remission of UC, rectal 5-ASA was not significantly different compared to oral 5-ASA. It has also been shown in clinical trials that topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent UC *(Ford et al 2012[b]).* Similarly, trials showed budesonide rectal foam was more effective than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis and patients with mild to moderate UC with distal active inflammation *(Sandborn et al 2015; Naganuma et al 2017).*
- According to the 2010 UC ACG guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine, and sulfasalazine. Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates and the combination of oral and topical agents is “superior” to each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone *(Kornbluth et al 2010).*
- The ACG guidelines recognize sulfasalazine as a first-line agent in the management of mild to moderately active colitis, and note balsalazide, mesalamine, olsalazine, and sulfasalazine as effective therapies for reducing the number of relapses and the maintenance of mild to moderate disease remission *(Kornbluth et al 2010).*
- The 2019 AGA guideline on the management of mild to moderate UC recommends standard-dose oral mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide, olsalazine) as first-line options for most patients. For management of left-sided ulcerative proctosigmoiditis or proctitis, mesalamine enemas or suppositories are suggested over oral mesalamine or rectal corticosteroids (*Ko et al 2019*).
- The 2018 ACG guideline on management of CD recommends controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD, but does not recommend use of budesonide beyond 4 months (*Lichtenstein et al 2018*).

- The differences in drug therapies (ie, pH-dependent parameters) allow for the tailoring of treatment based upon an individual's disease location and severity.
- Overall, oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine.

REFERENCES

- American College of Gastroenterology. Clinical Guidelines – Ulcerative Colitis in Adults. http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/. Accessed February 18, 2019.
- Apriso [package insert], Raleigh, NC: Salix Pharmaceuticals, Inc.; September 2018.
- Asacol HD [package insert], Irvine, CA: Allergan USA, Inc.; April 2018.
- Azulfidine EN-tabs [package insert], New York, NY: Pfizer; June 2016.
- Azulfidine [package insert], New York, NY: Pfizer; June 2016.
- Bernstein C, Eliakim A, Fedail S, et al. World Gastroenterology Organisation global guidelines on inflammatory bowel disease. Updated August 2015. http://www.worldgastroenterology.org/UserFiles/file/guidelines/inflammatory-bowel-disease-english-2015.pdf. Accessed February 18, 2019.
- Canasa [package insert], Irvine, CA: Allergan USA, Inc.; July 2017.
- Centers for Disease Control and Prevention (CDC). Epidemiology of the IBD. March 31, 2015. http://www.cdc.gov/ibd/ibd-epidemiology.htm. Accessed February 18, 2019.
- Centers for Disease Control and Prevention (CDC). Data and Statistics - IBD. November 14, 2018. http://www.cdc.gov/ibd/ibd-epidemiology.htm. Accessed February 18, 2019.
- Cheifetz AS, Cullen GJ. Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease. UpToDate Web site. www.uptodate.com. Updated April 11, 2018. Accessed February 18, 2019.
- Colazal [package insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc.; June 2016.
- Delzicol [package insert], Irvine, CA: Allergan USA, Inc.; January 2019.
- Dipentum [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; January 2014.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 18, 2019.
- Entocort EC [package insert], Allegan, MI: Perrigo Pharma International; January 2019.
- Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol.* 2017;112:241-58.
- Feagan BG, Chande N, MacDonald JK. Are there differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane Reviews. *Inflamm Bowel Dis*. 2013;19(9):2031-40.
- Feagan BG, MacDonald JK. Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis. *Inflamm Bowel Dis*. 2012;18:1785-1794.
- Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in UC: Systematic review and meta-analysis. *Am J Gastroenterol*. 2012[a];107:167-76.
- Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent UC: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012[b];10:513-9.
- Geremia A, Biancheri P, Allan P, et al. Innate and adaptive immunity in inflammatory bowel disease. *Autoimmun Rev*. 2014 Jan;13(1):3-10.
- Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology*. 2019;156(3):748-764. doi: 10.1053/j.gastro.2018.12.009.
- Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. UC practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010 Mar;105(3):501-23.
- Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014, Issue 8. Art. No.: CD0002913. doi: 10.1002/14651858.CD002913.pub3.
- Lialda [package insert], Lexington, MA: Shire US, Inc.; May 2018.
- Lichtenstein GR, Loftus EV, Isaacs, KL, Regueiro, MD, Gerson, LB, Sands, BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517. doi: 10.1038/ajg.2018.27.
- Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD Parenthood Project Working Group. *Gastroenterology*. 2019. [Epub ahead of print] doi: 10.1053/j.gastro.2018.12.022.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012, Issue 11. Art No.: CD004118. DOI: 10.1002/14651858.CD004118.pub2.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2010, Issue 1. Art. No.: CD004115. DOI: 10.1002/14651858.CD004115.pub2.
- Micromedex Healthcare Series Web site. http://www.micromedexsolutions.com/home/dispatch. Accessed February 18, 2019.
- Naganuma M, Aoyama N, Tada T, et al. Complete mucosal healing of distal lesions induced by twice-daily budesonide 2-mg foam promoted clinical remission of mild-to-moderate ulcerative colitis with distal active inflammation: double-blind, randomized study [published online ahead of print August 4, 2017]. *J Gastroenterol*. doi: 10.1007/s00535-017-1376-4.
- Nguyen NH, Fumery M, Dulai PS, et al. Comparative efficacy and tolerability of pharmacological agents for management of mild to moderate ulcerative colitis: a systematic review and network meta-analyses. *Lancet Gastroenterol Hepato*l. 2018;3(11):742-753. doi: 10.1016/S2468-1253(18)30231-0.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 18, 2019.
- Pentasa [package insert], Lexington, MA: Shire US, Inc.; May 2018.
- Peppercorn MA, Cheifetz AS. Definition, epidemiology, and risk factors in inflammatory bowel disease. UpToDate Web site[a]. www.uptodate.com. Updated November 12, 2018. Accessed February 18, 2019.

- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. UpToDate Web site[b]. www.uptodate.com. Updated November 19, 2018. Accessed February 18, 2019.
- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. UpToDate Web site[c]. www.uptodate.com. Updated November 20, 2018. Accessed February 18, 2019.
- Rezaie A, Kuenzig ME, Benchimol E, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015, Issue 6. Art. No.: CD000296. doi: 10.1002/14651858.CD000296.pub4.
- Rowasa [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; July 2017.
- Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. *Gastroenterology*. 2015;148(4):740-750.
- sfRowasa [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; July 2017.
- Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2015, Issue 10. Art. No.: CD007698. DOI: 10.1002/14651858.CD007698.pub3.
- Tong JL, Huang ML, Xu XT, et al. Once-daily vs multiple-daily mesalamine for patients with ulcerative colitis: a meta-analysis. *J Dig Dis*. 2012;13:200-7.
- Uceris extended-release tablet [package insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc; February 2018.
- Uceris rectal foam [package insert], Bridgewater, NJ: Salix pharmaceuticals, Inc.; September 2016.
- Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016[a], Issue 4. Art. No.: CD000543. DOI: 10.1002/14651858.CD000543.pub4.
- Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016[b], Issue 5. Art. No.: CD000544. DOI: 10.1002/14651858.CD000544.pub4.
- Zhu Y, Ren-kuan T, Zhao P, et al. Can oral 5-aminosalicyclic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials. *Eur J Gastroenterol Hepatol*. 2012;24:487-494.

Publication Date: March 25, 2019