



## Ulcerative Colitis Agents Therapeutic Class Review (TCR)

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May 11, 2022

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
<b>Oral Prodrug Forms</b>			
balsalazide (Colazal®) <sup>1</sup>	generic, Salix	Mild to moderately active ulcerative colitis (UC) in patients ≥ 5 years	--
olsalazine (Dipentum®) <sup>2</sup>	Meda/Mylan	--	Maintenance of remission of UC in patients intolerant of sulfasalazine
sulfasalazine (Azulfidine®, Azulfidine EN-tabs®) <sup>3,4</sup>	generic*, Pfizer	Mild to moderately active UC Adjunctive therapy in severe UC	Maintenance of remission of UC
		Other: Enteric-coated tablets are indicated in patients with UC who cannot take uncoated sulfasalazine tablets because of gastrointestinal (GI) intolerance Treatment of rheumatoid arthritis that has not responded adequately to salicylates or other nonsteroidal anti-inflammatory agents (NSAIDs) Treatment of pediatric patients with polyarticular juvenile rheumatoid arthritis who have not responded adequately to salicylates or other NSAIDs	
<b>Oral Delayed-Release Forms</b>			
mesalamine delayed-release tablets (Asacol® HD) <sup>5†</sup>	generic, Allergan	Moderately active UC	--
mesalamine delayed-release capsules (Delzicol®) <sup>6‡</sup>	generic, Allergan	Mild to moderately active UC in patients ≥ 5 years	Maintenance of remission of UC in adults
mesalamine MMX delayed-release tablets (Lialda®) <sup>7</sup>	generic, Shire US	Mild to moderately active UC in pediatric patients ≥ 24 kg and adults	Maintenance of remission of mild to moderately active UC in adults
mesalamine extended-release capsules (Pentasa®) <sup>8</sup>	generic, Shire US	Mild to moderately active UC	--
mesalamine extended-release capsules (Apriso®) <sup>9</sup>	generic, Salix	--	Maintenance of remission of UC in adults

### FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
<b>Rectal Forms</b>			
budesonide rectal foam (Uceris®) <sup>10</sup>	Salix	Mild to moderate active UC extending up to 40 cm from the anal verge	--
mesalamine enemas (Rowasa®) <sup>11</sup>	generic, Meda/Mylan	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine enemas sulfite-free (sfRowasa®) <sup>12</sup>	generic, Meda/Mylan	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine suppositories (Canasa®) <sup>13</sup>	generic, Allergan	Mild to moderate active ulcerative proctitis	--
<b>Oral Corticosteroids</b>			
budesonide extended-release tablets (Uceris®) <sup>14</sup>	generic, Santarus	Mild to moderately active UC	--

\* Only an authorized generic is available for Azulfidine EN-tabs.

†Dibutyl phthalate in the enteric coating of Asacol HD delayed release tablets has been replaced by dibutyl sebacate.

‡Delzicol delayed-release capsules are bioequivalent to Asacol; however, Delzicol is not AB-rated to Asacol as they are different formulations.

## OVERVIEW

Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colon and rectum.<sup>15</sup> The disease is characterized by superficial infiltration of the bowel wall by inflammatory white blood cells, resulting in mucosal ulcerations and crypt abscesses. The lesions are contiguous, typically extending retrograde from the rectum, involving the descending, transverse, or the entire colon (pancolitis). Long-term colonic inflammation due to UC increases the risk for colorectal cancer.<sup>16</sup>

UC affects approximately 1,000,000 people in the United States (US), and the incidence continues to increase worldwide.<sup>17</sup> In North America, the prevalence of UC is estimated to be 249 per 100,000 individuals.<sup>18</sup> UC may present at any age, but onset typically peaks between 15 and 30 years of age.<sup>19</sup>

The predominant symptoms of UC are diarrhea, urgency, tenesmus, and hematochezia (blood with the passage of stool).<sup>20</sup> Bowel movements are frequent but small in volume due to rectal inflammation.<sup>21</sup> Some patients suffer from pain in the lower quadrant or rectum. Systemic features, including fever, malaise, and weight loss, are more common if a greater portion of the colon is affected. The initial episode of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea. UC can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine. Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a small percentage of patients suffer a chronic continuous course. Diagnosis is confirmed by lower endoscopy evidence of continuous inflammation starting at the rectum and extending proximally; disease activity is then stratified as mild, moderate, severe, or fulminant utilizing a validated scoring tool (e.g., Mayo score for UC

activity).<sup>22,23</sup> The principal goal of UC treatment is inducing, then maintaining, steroid-free remission of the disease. To increase the likelihood of steroid-free remission and prevent hospitalizations and surgery, the American College of Gastroenterology (ACG) recommends treating to achieve mucosal healing.

Aminosalicylates are drug products containing the active ingredient 5-aminosalicylic acid (5-ASA). Aminosalicylates, including sulfasalazine, mesalamine, olsalazine, and balsalazide, remain first-line treatment options for mild to moderate active UC with 90% of patients treated with this class shortly after disease diagnosis.<sup>24</sup> Several aminosalicylates are available and differ only in mode of distribution throughout the small intestine and colon. Mesalamine agents are currently available in oral and rectal formulations. The rectal products achieve high luminal concentrations of 5-ASA in the distal colon making them an ideal treatment option for left-sided colitis and proctitis.<sup>25,26</sup>

The 2013 American Academy of Family Physicians (AAFP) guidelines for the diagnosis and treatment of UC state that the incidence of colon cancer is increased with UC and achieving remission is critical in order to reduce a patient's lifetime risk.<sup>27</sup> The guidelines recommend 5-ASA (mesalamine) via suppository or enema as first-line for patients with proctitis or proctosigmoiditis, respectively; patients unable to tolerate rectally administered 5-ASA therapy may try oral preparations, although response times and remission rates may not be as favorable. Oral 5-ASA is effective in patients with active mild to moderate UC extending from the proximal to the sigmoid colon; a topical 5-ASA may be added if an oral formulation alone is inadequate. A short-term course of oral corticosteroids may be appropriate if oral plus topical 5-ASA therapy is not effective or if a more rapid response is desired. Prednisone is given in dosages of 40 mg to 60 mg per day, with the full-dose continued until symptoms are completely controlled (usually 10 to 14 days) followed by a gradual taper. Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with IV infliximab (Remicade, biosimilars). A meta-analysis reported no statistically significant effect of azathioprine (Imuran®) for active UC and consistent data is lacking that reports adequate effect of azathioprine for preventing relapse. Azathioprine is generally not recommended for active UC; however, it may be considered in patients who require corticosteroids or cyclosporine to induce remission. The agent that is used to maintain remission is usually the same as that used to achieve remission. To prevent relapse of the disease, the oral probiotics *Lactobacillus* GG and *Escherichia coli* Nissle 1917 have been shown to be as effective as 5-ASA. Long-term steroid use is not recommended for chronic maintenance due to significant side effects. Budesonide (Uceris) was first FDA approved in January 2013 and is not specifically addressed in these guidelines. Adalimumab, golimumab, vedolizumab, ustekinumab, and tofacitinib were not FDA-approved to treat UC at the time these guidelines were developed.

The 2019 American College of Gastroenterology (ACG) clinical guidelines state treatment selection for UC should be based on not only inflammatory activity but also disease prognosis.<sup>28</sup> In general, mildly active proctitis and left-sided colitis are treated with a rectal 5-ASA preparation (Grade: strong, Level of evidence: high or moderate). Oral 5-ASA agents may be used concurrently for mildly active left-sided UC (conditional, low). For mildly active extensive disease, oral 5-ASA agents are recommended first line (strong, moderate). In patients with mildly to moderately active UC, non-responsive to 5-ASA, oral budesonide multi-matrix (MMX) (Uceris) is recommended to induce remission (strong, moderate). Moderately active UC should be treated with a non-systemic steroid like budesonide MMX (strong, moderate). Response to induction therapy should be evaluated within 6 weeks. With the exception of corticosteroids, the medication used to induce remission should be continued as maintenance therapy.

The ACG states that complimentary therapies such as probiotics, curcumin, and fecal microbiota transplantation (FMT) require further study and clarification of treatment endpoints.

The American Gastroenterological Association (AGA) 2019 practice guidelines for the treatment of mild to moderate UC **have been retired** but recommend standard-dose mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide and olsalazine) for induction and maintenance treatment in patients with extensive mild to moderate UC (Recommendation strength: strong, Quality of evidence: moderate).<sup>29</sup> High-dose oral mesalamine combined with rectal 5-ASA may be required for patients with suboptimal response to standard-dose therapy, or in those with moderate or extensive disease (conditional, moderate [induction]). Oral prednisone or budesonide MMX may be added in those refractory to optimized oral and rectal 5-ASA (conditional, low). Proctosigmoiditis or proctitis can be treated with topical mesalamine rather than oral 5-ASA (conditional, very low); in patients with suboptimal response or intolerance to rectal mesalamine, rectal corticosteroids (enema or foam) may be used (conditional, low). Patients who do not respond adequately to the therapies as outlined above may need to escalate to systemic corticosteroids, immunomodulators, or biologic therapies. Due to associated toxicity, the duration of systemic corticosteroids should be limited with a tapering plan guided by symptoms, onset of action of maintenance therapy, and cumulative steroid exposure. The guidelines make no recommendations regarding the use of probiotics, curcumin, and FMT; while they appear to be safe, their use could delay initiation of proven efficacious treatments and potentially lead to worsening symptoms or complications.

The 2020 AGA practice guidelines for moderate to severe UC consider patients with moderate to severe disease to be those who are dependent on or refractory to corticosteroids, exhibit ulcers upon endoscopic assessment, or are at high risk for colectomy.<sup>30</sup> For moderate to severe UC, the guidelines recommend first-line treatment with infliximab (Remicade<sup>®</sup>, biosimilars), adalimumab (Humira<sup>®</sup>), golimumab (Simponi<sup>®</sup>), vedolizumab (Entyvio<sup>®</sup>), tofacitinib (Xeljanz<sup>®</sup>, Xeljanz<sup>®</sup> XR), or ustekinumab (Stelara<sup>®</sup>). These drugs are all categorized as biologics, except for tofacitinib, which is a small molecule agent. The injectable tumor necrosis factor (TNF)-inhibitors, infliximab, adalimumab, and golimumab are approved for inducing and maintaining clinical response/remission in patients with moderate to severe active UC.<sup>31,32,33</sup> Infliximab and golimumab are only indicated in patients with an inadequate response to conventional therapy. Vedolizumab is an intravenous (IV) integrin receptor antagonist indicated in adults for the treatment of moderately to severely active UC.<sup>34</sup> The injectable interleukin-12/interleukin-23 antagonist, ustekinumab (Stelara<sup>®</sup>), received FDA approval for the treatment of adults with moderately to severely active UC in 2019.<sup>35</sup> The oral Janus kinase (JAK) inhibitor tofacitinib (Xeljanz<sup>®</sup>, Xeljanz XR) is indicated for adults with moderately to severely active UC, specifically for patients with an inadequate response or intolerance to TNF inhibitors.<sup>36</sup> Long-term management of patients with moderate to severe disease can include biologic agents, tofacitinib, or immunomodulators (e.g., azathioprine, methotrexate). The quality of evidence for induction and maintenance of remission with immunomodulators is lower than the evidence available for the biologics. If the agent selected for inducing remission is effective, it is usually continued as maintenance therapy; the exception to this would be when corticosteroids or cyclosporine are used for induction of remission. For patients who achieve remission with biologic agents and/or immunomodulators or tofacitinib, experts recommend against continuing 5-ASA for induction and maintenance of remission (conditional, very low). Agents indicated for moderate to severe UC are reviewed in a separate therapeutic class review. The AGA has also published a Clinical Decision Support Tool (Clinical Care Pathway) to correspond with the pharmacological management of outpatient adults

with moderate to severely active UC.<sup>37</sup> Ozanimod (Zeposia®), a sphingosine-1-phosphate receptor modulator, received approval in 2021 for the treatment of moderately to severely active ulcerative colitis in adults; after publication of all current guidelines.<sup>38</sup>

## PHARMACOLOGY<sup>39,40,41,42,43,44,45,46,47,48,49,50,51,52</sup>

The first oral aminosalicylate developed, sulfasalazine, consists of a sulfapyridine carrier moiety linked to 5-ASA via an azo bond.<sup>53</sup> Colonic bacteria cleave the azo bond, converting sulfasalazine into sulfapyridine and 5-ASA moieties.<sup>54</sup> While the sulfapyridine is absorbed and excreted in the urine, the 5-ASA component stays in the colon and is excreted in the feces. The anti-inflammatory activity is believed to be related to the inhibition of cyclooxygenase, and subsequently arachidonic acid, by 5-ASA, thereby diminishing the production of inflammatory prostaglandins. Mucosal production of arachidonic acid metabolites, through cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease. Inhibition of mucosal leukotriene synthesis, disruption of migration of polymorphonuclear leukocytes, as well as reduction of interleukin-1, interleukin-2, and tumor necrosis factor (TNF) may also be components of 5-ASA activity.<sup>55,56</sup>

Subsequent oral agents were developed to enhance 5-ASA delivery to the colon and reduce the incidence of adverse events.<sup>57</sup> The formulations fall into 4 categories: azo-bonded prodrug formulations (Colazal, Dipentum), pH-dependent delayed-release formulations (Asacol HD, Delzicol), extended-release formulations (Apriso, Lialda), or controlled-release formulations (Pentasa). The azo-bonded prodrugs are similar to sulfasalazine, as colonic bacteria are required to cleave the azo bond and release the active 5-ASA moiety.<sup>58</sup> With these drugs, 5-ASA is delivered only to the colon. In the delayed-release formulations, which are dosed 3 times a day, the acrylic-base resin dissolves at pH  $\geq 7$ , delivering 10% to 15% of 5-ASA to the terminal ileum of the small intestine and the remainder to the colon. Extended-release drugs are also pH-dependent but allow for once daily dosing due to an outer coating that dissolves at pH  $\geq 6$  in the distal ileum and slowly releases mesalamine throughout the colon. Apriso uses Intellicor® technology with an outer coating that dissolves at a  $\geq$  pH 6 releasing mesalamine granules with a delayed transit time through the colon.<sup>59</sup> Lialda DR tablets use an extended-release Multi Matrix System® (MMX) technology, a pH-dependent polymer film which dissolves at pH  $\geq 6.8$  allowing for a slow release of mesalamine from the tablet core from the terminal ileum through the colon.<sup>60</sup> With controlled-release preparations, 5-ASA release is time dependent and 30% to 40% is released in the duodenum, with the remainder of active drug being delivered through the small intestine and colon.<sup>61</sup> Effectiveness of delayed and controlled-release formulations may be variable due to individual physiology Drug delivery to the area of inflammation is dependent upon gastric emptying, transit time through the small intestine, and intraluminal pH.<sup>62</sup>

In December 2012, the FDA issued a final guidance recommending against the use of 2 specific phthalates, dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP), as excipients due to developmental and reproductive toxicants in laboratory animals, potential for being endocrine disrupting, and affecting reproductive and developmental outcomes in humans.<sup>63,64</sup> These agents are often used as plasticizers in enteric and delayed release coatings of drug products, including a mesalamine delayed-release product (Asacol HD). Two formulations of mesalamine DR, Asacol HD and Delzicol, have been reformulated without DBP; DBP has been substituted with dibutyl sebacate (DBS).

Mesalamine is available as suppositories (Canasa) and enemas that deliver 5-ASA directly to the site of action. For the treatment of ulcerative proctitis, mesalamine suppositories (or corticosteroid foam),

which deliver drug to the rectum, are appropriate for treatment of diseased colon within 18 cm of the anal verge.<sup>65,66</sup> Mesalamine (or corticosteroid) retention enemas, which distribute drug to the left colon, can be used for active disease involving up to 60 centimeters of distal colon.<sup>67</sup> A sulfite-free formulation of mesalamine enema (sfRowasa) has been FDA-approved.<sup>68</sup> Tolerability of rectal formulations is variable based on an individual patient's ability to retain the drug preparation for the allotted time.<sup>69</sup>

Steroids, such as budesonide ER (Uceris), may suppress autoimmune and inflammatory responses in UC.<sup>70</sup> Budesonide has a high topical glucocorticosteroid activity and substantial first-pass elimination. Uceris is a delayed and extended-release tablet using MMX technology that resists gastric acid and breaks down at pH  $\geq$  7. The inner drug matrix releases budesonide gradually through the colon. Budesonide is also available as rectal foam (Uceris rectal foam) and can be used for active mild to moderate distal ulcerative colitis extending up to 40 centimeters from the anal verge.<sup>71</sup>

## **PHARMACOKINETICS**<sup>72,73,74,75,76,77,78,79,80,81,82,83,84,85</sup>

All aminosalicylate oral products are designed to release 5-ASA for action in the intestine; therefore, systemic absorption is intended to be minimal. Absorbed 5-ASA and its metabolites are excreted in the urine. The majority of 5-ASA remains in the colonic lumen and is excreted in feces. The apparent half-life of 5-ASA can range from 2 to 15 hours due to the different formulations of the drugs.

## Pharmacokinetics

Drug	Delivery Mechanism	Bioavailability (%)
<b>Oral Prodrug Forms</b>		
balsalazide (Colazal)	Delivered to the colon intact then bacteria cleave the compound to release 5-ASA	low and variable
olsalazine (Dipentum)	Rapidly converted in the colon to molecules of 5-ASA by bacteria and the colon's low prevailing redox potential	2.4
sulfasalazine (Azulfidine, Azulfidine EN-Tabs)	Metabolized by intestinal bacteria to 5-ASA and sulfapyridine; site of delivery is the colon Azulfidine EN-Tabs contain a cellulose acetate phthalate coating that retards disintegration in the stomach	< 15
<b>Oral Delayed-Release Forms</b>		
mesalamine delayed-release tablets (Asacol HD)	Acrylic-based resin coating delays 5-ASA release until tablet reaches the terminal ileum and beyond; pH dependent release at pH $\geq$ 7	20–25
mesalamine delayed-release capsules (Delzicol)*	Capsules contain acrylic based resin, which delays 5-ASA release until capsule reaches the terminal ileum and beyond; pH-dependent release at $\geq$ pH 7	28
<b>Oral Delayed-Release Forms (continued)</b>		
mesalamine MMX tablets (Lialda)	pH-dependent polymer film breaks down at pH $\geq$ 6.8, in terminal ileum where mesalamine begins to be released from tablet core; tablet core has hydrophilic and lipophilic excipients that provide an extended release of mesalamine	21–22
mesalamine extended-release capsules (Pentasa)	Ethylcellulose-coated, controlled-release formulation releases 5-ASA throughout the intestinal tract	20–30
mesalamine extended-release capsules (Apriso)	Intellicor extended-release delivery technology that combines an enteric pH-dependent coating which provides a delayed release starting at a pH of 6 with a polymer matrix core that enables extended release	21–44
<b>Rectal Forms</b>		
budesonide rectal foam (Uceris)	Rectal administration	60
mesalamine enemas (Rowasa, sfRowasa)	Rectal administration	10–30
mesalamine suppositories (Canasa)	Rectal administration	variable
<b>Oral Corticosteroids</b>		
budesonide extended-release tablets (Uceris)	pH dependent enteric coated delayed-release tablets with a polymer coating that dissolves at pH $\geq$ 7 with an extended-release tablet core	10–20

\* Delzicol 400 mg capsules are bioequivalent to Asacol 400 mg tablets. Two Delzicol 400 mg capsules have not been shown to be bioequivalent to 1 Asacol HD 800 mg tablets.

## CONTRAINDICATIONS/WARNINGS<sup>86,87,88,89,90,91,92,93,94,95,96,97,98,99</sup>

Aminosalicylates are contraindicated in patients with salicylate hypersensitivity. Mesalamine-containing products and mesalamine prodrugs are also contraindicated in patients with a hypersensitivity to salicylates, aminosalicylates, or any of the other components. Hypersensitivity reactions to mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa) may include myocarditis or pericarditis. Olsalazine (Dipentum) is contraindicated in patients with hypersensitivity to salicylates, aminosalicylates or their metabolites, or to any of the excipients. Sulfasalazine is also contraindicated in patients with sulfonamide hypersensitivity, porphyria, and intestinal or urinary obstruction. Budesonide ER (Uceris) is contraindicated in patients hypersensitive to budesonide or any excipients in of the product.

Mesalamine enema (Rowasa rectal suspension enema) contains potassium metabisulfite, a sulfite which may cause life-threatening allergic-type reactions including anaphylaxis. Sulfite sensitivity is more frequent in asthmatic patients or atopic non-asthmatic persons. Overall prevalence of sulfite sensitivity in the general population is not known, but probably low. A sulfite-free mesalamine enema (sfRowasa) is available; it is proposed to be safe for use in patients with sulfite allergy but still carries a contraindication regarding use in patients with known or suspected hypersensitivity to sulfites.

Deaths associated with administration of sulfasalazine have been reported. Deaths occurred from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, serious infections, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. Complete blood counts, as well as urinalysis with careful microscopic examination, should be performed frequently in patients receiving sulfasalazine. Oligospermia and infertility have been observed in men treated with sulfasalazine; however, withdrawal of the drug appears to reverse the effects. Patients with a hypersensitivity reaction to sulfasalazine may have a similar reaction to other compounds that contain mesalamine (e.g., Pentasa, Rowasa, Lialda, Apriso) or are converted to mesalamine (e.g., Colazal, Dipentum). These hypersensitivity reactions can manifest as myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Sulfasalazine should be given with caution to patients with severe allergic conditions or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Dose-related hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase deficiency.

Renal impairment, including acute and chronic interstitial nephritis and renal failure, has been reported in patients taking products that contain, or are converted to, mesalamine. Evaluate renal function prior to initiation of therapy and periodically thereafter. The risks and benefits of using mesalamine delayed-release products should be evaluated in patients with known renal impairment or taking nephrotoxic drugs. Nephrolithiasis has occurred with the use of mesalamine (e.g., Apriso, Asacol HD, Canasa, Delzicol, Lialda, Pentasa, Rowasa, sfRowasa); as a result, adequate hydration is important when taking mesalamine and mesalamine prodrugs (e.g., balsalazide [Colazal], olsalazine [Dipentum]). Patients with pyloric stenosis may have prolonged gastric retention of oral mesalamine and balsalazide, which could delay the release of drug in the colon. Product labeling for the mesalamine formulation, Lialda, states it should be avoided in patients at risk of upper gastrointestinal tract obstruction. Hepatic failure has occurred in patients with pre-existing liver disease who have taken mesalamine. Since balsalazide and olsalazine are both converted to mesalamine, the risks and benefits of using these agents should also be assessed in patients with existing liver impairment. Lastly, mesalamine, balsalazide, and olsalazine

have been associated with an acute intolerance syndrome that may be difficult to distinguish from a UC flare. These symptoms may abate once the agent is discontinued.

Severe and sometimes fatal cutaneous adverse reactions have been reported with mesalamine and sulfasalazine, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Mesalamine products, mesalamine prodrugs, and sulfasalazine should be discontinued at the first signs of hypersensitivity or severe cutaneous reactions. Fever and lymphadenopathy are early manifestations of hypersensitivity which should be addressed even if rash is not present.

Mesalamine, a metabolite of sulfasalazine, may spuriously elevate test results for urinary normetanephrine when measured by liquid chromatography with electrochemical detection when testing for pheochromocytoma. Balsalazide (Colazal) and olsalazine (Dipentum) also carry this potential.

Mesalamine (Apriso, Asacol HD, Canasa, Delzicol, Lialda, Pentasa, Rowasa, sfRowasa), balsalazide (Colazal), and olsalazine (Dipentum) have warnings of photosensitivity reactions for patients who have pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Two mesalamine products, Asacol HD and Delzicol, have warnings regarding the associated iron contents of the products. Iron oxide is used as the colorant in the coating of the delayed-release (DR) Asacol HD tablets and Delzicol capsules. Precaution should be taken in patients receiving iron supplementation or in those at risk of developing iron overload.

Chronic glucocorticosteroid use may cause hypercorticism, adrenal suppression, and can reduce the response of the hypothalamus-pituitary adrenal (HPA) axis to stress, such as surgery. Patients who are switched from glucocorticosteroids with greater systemic effects may undergo withdrawal, including acute adrenal suppression or benign intracranial hypertension. Consequently, adrenocortical function should be monitored and the dose of the high potency glucocorticosteroid should be reduced cautiously. Glucocorticoids can also suppress the immune system causing increased susceptibility to infection. Consequently, exposure to transmissible diseases should be avoided and corticosteroid use in patients with active or quiescent tuberculosis infection or untreated fungal, bacterial, or systemic viral or parasitic infections should be done cautiously, if at all. Liver dysfunction may decrease elimination and increase bioavailability resulting in increased toxicity. Caution should be observed in patients with hypertension, diabetes, osteoporosis, peptic ulcer, glaucoma, or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticoids may have unwanted effects.

## **DRUG INTERACTIONS**<sup>100,101,102,103,104,105,106,107,108,109,110,111,112,113</sup>

CYP3A4 inhibitors: Concomitant oral administration of budesonide ER (Uceris) and ketoconazole (a strong CYP3A4 inhibitor) causes an 8-fold increase in the systemic exposure to oral budesonide ER. If treatment with inhibitors of CYP3A4 activity (e.g., ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, prior discontinuation of budesonide ER should be considered. Ingestion of grapefruit juice (which predominantly inhibits intestinal mucosal CYP3A4), increased systemic exposure for oral budesonide ER about 2-fold. Consequently, ingestion of grapefruit or grapefruit juice should be avoided with budesonide ER administration. Similarly, the inhibitors of

CYP3A4 previously noted may increase systemic budesonide concentrations and should be avoided with budesonide rectal foam.

Digoxin: Sulfasalazine, in doses > 2 g daily, reduces the oral absorption of digoxin by 25%. It is unclear if other aminosalicylates have any significant effect on digoxin absorption.

Drugs that alter gastric pH: Mesalamine ER capsules (Apriso) depend on pH for dissolution of the coating of the granules; therefore, concomitant use with antacids should not occur. Dissolution of the coating of budesonide ER tablets (Uceris) is pH dependent. Consequently, drug release and absorption may be altered when budesonide ER is used with drugs that raise gastric pH (e.g., proton pump inhibitors [PPIs], histamine 2- [H2]-blockers, and antacids).

Folic acid: Sulfasalazine can inhibit the absorption of folic acid; supplementation of folic acid may be required.

Warfarin and low molecular weight heparins (LMWH)/heparinoids: Increased prothrombin time has been reported in patients taking olsalazine and warfarin; monitor international normalized ratio (INR) and prothrombin time with dose adjustments of warfarin, as necessary. Patients taking salicylates, including olsalazine, and LMWH or heparinoids may be at an increased risk of bleeding following neuraxial anesthesia. Salicylates should be discontinued before initiation of a heparin-derivative anticoagulant.

Nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs): Mesalamine use with known nephrotoxic agents may increase the risk of renal reactions and mesalamine-related adverse effects. This interaction also applies to balsalazide (Colazal) and olsalazine (Dipentum) as both drugs are converted to mesalamine.

Azathioprine, 6-mercaptopurine, and other myelosuppressive agents (e.g., thioguanine): Mesalamine use with these drugs may increase the risk for blood disorders, bone marrow failure, and related complications. This interaction also applies to the mesalamine prodrugs, balsalazide (Colazal) and olsalazine (Dipentum).

Varicella vaccine: Salicylates (e.g., olsalazine) should not be administered for 6 weeks after the varicella vaccine due the potential risk of developing Reye's syndrome.

## ADVERSE EFFECTS<sup>114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129</sup>

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
<b>Oral Prodrug Forms</b>							
balsalazide (Colazal)	6–13 (3)	5–9 (3)	2–6 (0)	8–15	4–5	nr	4–10
olsalazine (Dipentum)	10.1 (7.2)	5.9–17 (4.8-6.7)	< 1	5 (4.8)	5 (3.9)	2.3 (1.4)	1
sulfasalazine (Azulfidine)	reported	reported	less common	more common	more common	less common	more common
sulfasalazine (Azulfidine EN-tabs)	8	reported	reported	9	19	13	8
<b>Oral Delayed-Release Forms</b>							
mesalamine DR (Asacol HD)	2.3	1.7	0.7	4.7	2.8	reported	1.4
mesalamine MMX tablets (Lialda)*	2	2	reported	3–6 (< 1)	< 1	1	< 1
mesalamine ER capsules (Pentasa)	1.1–1.7 (4)	3.5 (7.5)	0.9 (1.2)	2.2 (3.5)	1.8–3.1	1.3 (1.2)	1.1–1.5
mesalamine ER capsules (Apriso)	5 (3)	8 (7)	reported	11 (8)	4 (3)	reported	nr
<b>Rectal Forms</b>							
budesonide rectal foam (Uceris)	nr	nr	reported	nr	2 (1)	reported	nr
mesalamine enemas (Rowasa, sfRowasa)	8.1 (7.8)	2.1 (3.9)	3.2 (0)	6.5 (12.5)	5.8 (9.4)	2.8 (3.1)	nr
mesalamine suppositories (Canasa)	5	3	1.2 (0)	14	3	1.2 (0)	reported
<b>Oral Corticosteroids</b>							
budesonide ER tablets (Uceris)	3.9 (1.9)	reported	nr	11.4 (10.5)	5.1 (4.3)	reported	nr

Adverse effects are reported as a percentage. Incidences reported for placebo group are shown in parentheses. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Adverse event rates with Delzicol are not available as approval was based on bioequivalence to Asacol and the data from the Asacol safety and efficacy studies.

\*Adverse reactions reported in adults

Clinical tolerance of 3 aminosalicylate preparations [mesalamine (Asacol), olsalazine (Dipentum), and balsalazide] was assessed in a consecutive series of 43 patients with inflammatory bowel disease intolerant to sulfasalazine.<sup>130</sup> Ninety-one percent of patients were able to tolerate at least 1 of the 3 preparations. Clinical tolerance of mesalamine (63%), olsalazine (70%), and balsalazide (70%) was similar. The most common adverse effects associated with the preparations were gastrointestinal in

nature; diarrhea was a problem in 5 patients during treatment with olsalazine and 3 each while on mesalamine and balsalazide. Allergic reactions to aminosalicylates were uncommon; of 10 patients with rash following sulfasalazine, only 1 developed a rash with mesalamine. Results of this study indicate the vast majority of patients with inflammatory bowel disease can be managed with at least 1 of the 4 aminosalicylates, and adverse effects of sulfasalazine are multifactorial in etiology. Some adverse effects are due to the parent molecule, and some to 1 of its 2 metabolites, 5-ASA and sulfapyridine.

Exacerbation of UC symptoms has been reported upon initiation of therapy with Asacol HD as well as other mesalamine products. These symptoms usually abate once Asacol HD is discontinued. Several other post-marketing adverse effects have been reported with various mesalamine formulations including nephrogenic diabetes insipidus, intracranial hypertension, lupus-like syndrome, hypersensitivity pneumonitis, interstitial lung disease, and hepatotoxicity.

Mesalamine (Lialda) has been evaluated in pediatric patients (n=105) aged 5 to 17 years and was found to have similar adverse reactions to observed in adults. The most common adverse effects ( $\geq 5\%$ ) of pediatric patients included abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection.

The sulfite-free mesalamine enema (sfRowasa) is proposed to cause less bowel irritation than the original Rowasa enema formulation.

In a pooled analysis of the two phase 3 clinical trials, there were no clinically significant differences in glucocorticoid-related adverse events between budesonide ER (Uceris) 9 mg and placebo at 8 weeks.

In the use of budesonide rectal foam, no clinically significant differences were reported in the overall percentage of glucocorticoid related adverse effects between budesonide foam and placebo over the course of 2 placebo-controlled trials at 6 weeks of therapy. Common adverse reactions (incidence  $\geq 2\%$ ) included decreased blood cortisol, adrenal insufficiency, and nausea.

## **SPECIAL POPULATIONS** [131,132,133,134,135,136,137,138,139,140,141,142,143,144](#)

### **Pregnancy**

The labeling for balsalazide capsules (Colazal), budesonide ER tablet (Uceris), budesonide rectal foam (Uceris), mesalamine (Asacol HD, Apriso, Delzicol, Lialda, Pentasa, Rowasa, sfRowasa), olsalazine (Dipentum), and sulfasalazine (Azulfidine) have been updated based on the Pregnancy and Lactation Labeling Rule (PLLR). All state that there are no adequate and well-controlled studies in pregnant women; therefore, the drug should only be used during pregnancy if clearly needed. There have been case reports of neural tube defects (NTDs) in infants born to mothers exposed to sulfasalazine during pregnancy. The role of sulfasalazine in these NTDs has not been established; however, oral sulfasalazine inhibits the absorption and metabolism of folic acid, which may interfere with folic acid supplementation. The labeling for mesalamine (Apriso, Asacol HD, Canasa) and budesonide rectal foam and extended-release tablet advises data are insufficient to inform of drug-associated risks in pregnant women.

### **Pediatrics**

Sulfasalazine is approved for use in patients  $\geq 6$  years of age. Mesalamine (Delzicol) is indicated for treatment of mild to moderate active ulcerative colitis in children age  $\geq 5$  years, but is not indicated for

maintenance therapy. Mesalamine (Lialda) is approved for use in treating mild to moderate active UC in pediatric patients weighing  $\geq 24$  kg, but it is not indicated for maintenance of remission. Efficacy of mesalamine suppositories (Canasa) was not demonstrated in a 6-week open-label study in patients 5 to 17 years of age with ulcerative proctitis (n=49). Balsalazide (Colazal) is approved for use in patients  $\geq 5$  years of age. Other products have not been sufficiently studied in pediatric populations.

Safety and effectiveness of oral budesonide ER (Uceris) as well as budesonide rectal foam (Uceris) have not been established in pediatric patients. Glucocorticosteroids, such as budesonide, may cause a reduction of growth velocity.

Product labeling for olsalazine (Dipentum) state that safety and effectiveness of in a pediatric population have not been established. However, in a 3-month double-blind, randomized trial that compared olsalazine to an equivalent dose of sulfasalazine in 56 children with mild to moderate UC, fewer patients on olsalazine improved and a greater number had progression of symptoms. Adverse effects were similar between the groups. For more detail of this study see the Clinical Trials section of this class review.

## Geriatrics

Data from uncontrolled clinical studies and postmarketing experience suggested a higher incidence of blood dyscrasias (e.g., agranulocytosis, neutropenia, pancytopenia) in patients  $\geq 65$  years old who were taking mesalamine-containing products and prodrugs; however, these events may also be associated with UC, concurrently administered drugs, or decreased kidney function. Caution should be taken to closely monitor blood cell counts (e.g., complete blood cell [CBC] counts, platelets) during therapy, especially if used concurrently with anticoagulants.

Clinical studies of budesonide ER (Uceris) and budesonide rectal foam (Uceris) did not include sufficient subjects aged  $\geq 65$  years to determine whether they respond differently in younger subjects. In general, budesonide ER should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and concomitant disease.

## Hepatic Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism with budesonide rectal foam (Uceris) and budesonide ER (Uceris). Labeling warns that sulfasalazine should only be administered to patients with hepatic insufficiency after significant consideration due to the risk of further organ damage with the medication. Mesalamine has also been associated with hepatic failure in patients with pre-existing liver disease.

## Renal Impairment

Mesalamine is excreted largely by the kidney, and therefore the risk for adverse events from mesalamine-containing products or prodrugs, may be higher in patients with renal dysfunction. Renal function should be assessed before starting therapy and regularly during treatment. Those with known renal impairment, history of renal disease, or using nephrotoxic drugs should be monitored for reduced renal function and mesalamine-related adverse reactions, if it is determined the benefits exceed the risks of therapy. Labeling warns that sulfasalazine should only be administered to patients with renal insufficiency after significant consideration due to the risk of further organ damage with the medication.

## **Gender**

Adverse effects such as abdominal pain, fatigue, and nausea were reported more frequently in women than in men with balsalazide capsules (Colazal).

## **Phenylketonuria (PKU)**

Caution should be taken when mesalamine ER (Apriso) is administered to patients with phenylketonuria because each capsule contains aspartame equivalent to 0.56 mg of phenylalanine.

## DOSAGES<sup>145,146,147,148,149,150,151,152,153,154,155,156,157,158</sup>

Drug	Adults	Pediatrics	Availability
<b>Oral Prodrug Forms</b>			
balsalazide (Colazal)	2.25 g (3 capsules) 3 times daily with or without food for 8 to 12 weeks; total daily dose: 6.75 g	Children 5 to 17 years: 2.25 g (three 750 mg capsules) 3 times daily for 8 weeks OR 750 mg (1 capsule) 3 times daily for 8 weeks*	750 mg capsule
olsalazine (Dipentum)	0.5 g (2 capsules) twice daily	--	250 mg capsule
sulfasalazine (Azulfidine, Azulfidine EN-tabs)	Initial: 3 to 4 g (6 to 8 tablets) daily in evenly divided doses with dosage intervals not exceeding 8 hours Maintenance: 2 grams daily	Children ≥ 6 years: Initial: 40 to 60 mg/kg/day divided into 3 to 6 doses Maintenance: 30 mg/kg per day divided into 4 doses	500 mg tablet 500 mg enteric coated delayed-release tablet
<b>Oral Delayed-Release Forms</b>			
mesalamine delayed-release tablets (Asacol HD) <sup>†</sup>	1.6 g (2 tablets) 3 times daily for 6 weeks <sup>‡</sup> ; total daily dose: 4.8 g; take on an empty stomach ≥ 1 hour before and 2 hours after a meal	--	800 mg delayed-release tablet
mesalamine delayed-release capsules (Delzicol) <sup>†</sup>	Initial: 0.8 g (2 capsules) 3 times daily with or without food for 6 weeks; total daily dose: 2.4 g Maintenance: 1.6 g (4 capsules) daily in 2 to 4 divided doses for 6 months <sup>§</sup>	Children ≥ 5 years: Initial: weight-based up to a maximum of 2.4 g/day with or without food; twice daily dosing for 6 weeks Maintenance: not indicated	400 mg delayed-release capsule
mesalamine MMX tablets (Lialda)	Initial Therapy: 2.4 g to 4.8 g (2 to 4 tablets) once daily with food for up to 8 weeks <sup>  </sup> Maintenance: 2.4 g (2 tablets) once daily with food	Children ≥ 24 kg: Initial: weight-based up to a maximum of 4.8 g/day with food; once daily for 8 weeks Maintenance: weight-based up to a maximum of 2.4 g/day	1.2 g delayed-release tablet

\* Balsalazide capsules (Colazal) may be opened and sprinkled on applesauce; contents may be chewed.

<sup>†</sup>Asacol HD and Delzicol have been formulated without dibutyl phthalate (DBP).

<sup>‡</sup> Safety and efficacy of mesalamine delayed-release (Asacol HD) past 6 weeks of treatment of UC have not been established.

<sup>§</sup> Mesalamine DR (Delzicol): swallow whole, do not chew, crush or break; for patients unable to swallow capsules whole, open the number of capsules required for the dose and swallow the contents whole.

<sup>||</sup> The study used for approval of mesalamine MMX delayed-release (Lialda) was based on use of the drug for induction of remission of UC for a period of 8 weeks.

### Dosages (continued)

Drug	Adults	Pediatrics	Availability
<b>Oral Delayed-Release Forms (continued)</b>			
mesalamine extended-release capsules (Pentasa)	1 g (2 to 4 capsules) 4 times a day for up to 8 weeks <sup>¶</sup>	--	250 mg, 500 mg extended-release capsules
mesalamine extended-release capsules (Apriso)	1.5 g (4 capsules) once daily in the morning with or without food <sup>**</sup>	--	0.375 g extended-release capsules
<b>Rectal Forms</b>			
budesonide rectal foam (Uceris)	1 metered dose (2 mg) rectally twice daily for 2 weeks followed by 1 metered dose once daily for 4 weeks	--	2 aerosol canisters each containing 14 metered doses (delivering 2 mg per actuation) with 28 PVC applicators
mesalamine enemas (Rowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of 8 hours) for 3 to 6 weeks	--	4 g/60 mL enema (7 and 28 unit packages) Kits include the suspension and cleansing wipes
mesalamine enemas sulfite-free (sfRowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of 8 hours) for 3 to 6 weeks	--	4 g/60 mL enema (7 and 28 unit packages)
mesalamine suppositories (Canasa)	1 g rectally at bedtime (and retained for a minimum of 1 to 3 hours) for 3 to 6 weeks	--	1,000 mg suppositories
<b>Oral Corticosteroids</b>			
budesonide ER tablets (Uceris) <sup>††</sup>	9 mg once daily in the morning with or without food for up to 8 weeks	--	9 mg enteric coated delayed- and extended-release tablets

¶ Mesalamine capsules (Pentasa): capsules may be swallowed whole or capsule may be opened and the contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. Capsules and contents must not be crushed or chewed.

\*\* The duration of mesalamine Intellicor extended-release (Apriso) use for maintaining remission of UC beyond 6 months has not been evaluated.

†† Budesonide ER (Uceris): swallow whole, do not chew, crush, or break.

## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

The safety and efficacy of Delzicol is based on the Asacol clinical trials.<sup>159</sup> Asacol has since been removed from the market, but studies including Asacol are included below because Asacol served as an active comparator for subsequent products.

### **balsalazide (Colazal) versus mesalamine delayed-release (Asacol)**

A double-blind study compared the effectiveness of balsalazide and mesalamine delayed-release (DR) in the treatment of 101 patients with active moderate to severe UC.<sup>160</sup> Patients were randomized to receive balsalazide 6.75 g/day or mesalamine DR 2.4 g/day for 12 weeks. After 2, 4, and 12 weeks, symptom control was greater in the balsalazide group. Remission rate after 12 weeks of therapy was 62% with balsalazide and 37% with mesalamine DR. Median time to first day of complete relief of symptoms was 10 days for the balsalazide group and 25 days for the mesalamine DR group. Adverse effects occurred in 48% of patients treated with balsalazide and 71% of those treated with mesalamine DR.

A randomized, double-blind, double-dummy, parallel-group, dose-response study was performed comparing balsalazide 2.25 g or 6.75 g daily and delayed-release mesalamine 2.4 g daily.<sup>161</sup> Medication was administered for 8 weeks to 154 patients with active, mild to moderate UC, the majority of whom were relapsing. High-dose balsalazide was superior to low-dose in rectal bleeding, stool frequency, sigmoidoscopic score, and Physician's Global Assessment (PGA). The only significant difference observed between high-dose balsalazide and mesalamine DR was more rapid onset of action as determined by a better 2-week sigmoidoscopic score for patients treated with balsalazide (55% versus 29%;  $p=0.006$ ). Balsalazide 6.75 g daily was well tolerated, and the safety profile did not differ significantly between balsalazide 2.25 g daily or mesalamine DR 2.4 g daily.

A total of 173 patients with active, mild to moderate UC were randomized to 8 weeks of double-blind treatment with balsalazide 2.25 g or mesalamine 0.8 g, each given 3 times daily.<sup>162</sup> Overall, 46% of balsalazide-treated and 44% of mesalamine-treated patients achieved symptomatic remission at endpoint. Although the median time to symptomatic remission was shorter with balsalazide (25 days) than with mesalamine (37 days), the difference was not clinically significant. Significantly more

balsalazide-treated patients showed improvement in sigmoidoscopic score ( $p=0.002$ ), stool frequency ( $p=0.006$ ), rectal bleeding ( $p=0.006$ ), and physician global assessment scores ( $p=0.013$ ) by 14 days compared to mesalamine-treated patients. The difference between groups in improved sigmoidoscopic score was significant at day 28 ( $p=0.002$ ). By day 56 and at endpoint, no significant differences between groups were detected. During the treatment period, 54% of balsalazide- and 64% of mesalamine-treated patients reported at least 1 treatment-emergent adverse event. The most common adverse events affected the gastrointestinal tract or the central and peripheral nervous systems.

The mesalamine delayed-release (Asacol) product used in the studies was manufactured and marketed by Smith Kline & French in the United Kingdom, rather than the Procter & Gamble product used in North America. Although the significance is not known, data are available from comparative *in vitro* dissolution studies to suggest slight differences exist between the 2 Asacol products.<sup>163</sup>

### **budesonide extended-release tablets (Uceris) versus placebo and budesonide**

This was a randomized, double-blind, placebo-controlled study in 461 adults with active, mild to moderate UC, defined as an Ulcerative Colitis Disease Activity Index (UCDAI) of  $\geq 4$  and  $\leq 10$  and histology consistent with active UC.<sup>164</sup> Budesonide ER 9 mg and budesonide ER 6 mg (not approved in the US) were compared with another brand of budesonide 9 mg (as reference) not approved for the treatment of UC, and compared to placebo. The primary endpoint was induction of remission after 8 weeks and remission was defined as a UCDAI score of  $\leq 1$ , with sub scores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a  $\geq 1$  point reduction in an endoscopy-only score. At the end of 8 weeks 17.4% in the budesonide ER 9 mg group, 8.3% in the budesonide ER 6 mg group, 12.6% in the budesonide 9 mg group, and 4.5% of placebo, were in remission. The difference in remission rate for budesonide ER 9 mg versus placebo was 12.9% (95% confidence interval [CI], 4.6 to 21.3,  $p<0.025$ ).

### **budesonide extended-release tablets (Uceris) versus placebo and mesalamine**

This was a randomized, double-blind, placebo-controlled study in 509 adult patients with active, mild to moderate UC.<sup>165,166</sup> Budesonide ER 9 mg and budesonide ER 6 mg (not approved in the US) were compared with mesalamine DR 2.4 g (as reference), and to placebo. The primary endpoint was induction of remission after 8 weeks. Remission was defined as a UCDAI score of  $\leq 1$ , with sub scores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a  $\geq 1$  point reduction in an endoscopy-only score. At the end of 8 weeks 17.9% of patients administered budesonide ER 9 mg, 13.2% in the budesonide ER 6 mg arm, 12.1% in the mesalamine DR 2.4 g arm, and 7.4% of placebo patients, were in remission. The difference in remission rate for budesonide ER 9 mg compared to placebo was 10.4% (95% CI, 2.2 to 18.7,  $p<0.025$ ). Adverse events occurred at similar rates among groups.

### **budesonide extended-release tablets (Uceris) plus oral mesalamine versus placebo plus oral mesalamine**

A randomized, double-blind, placebo-controlled, multicenter trial assessed the efficacy and safety of budesonide ER for induction of remission in 510 adults with mild to moderate ulcerative colitis (UC) refractory to mesalamine therapy.<sup>167</sup> Patients were randomized to either once daily oral budesonide 9 mg or placebo for 8 weeks. Patients also continued baseline treatment with oral mesalamine  $\geq 2.4$  g/day. An intention-to-treat (ITT) analysis found that clinical and endoscopic remission was achieved by

the end of 8 weeks in 13% of patients receiving budesonide compared to 7.5% of patients receiving placebo (p=0.049). In patients receiving budesonide versus placebo, more patients achieved endoscopic remission (20% versus 12.3 %, respectively; p=0.02) and histological healing (27% versus 17.5%, respectively; p=0.02). However, clinical remission as measured by UCDAI rectal bleeding and stool frequency subscale scores of 0 was similar in both groups (p=0.7). Adverse effect rates were similar between the budesonide group and placebo (31.8% versus 27.1%; p=0.02).

### **budesonide rectal foam (Uceris) versus placebo**

Two randomized, double-blind, placebo-controlled, multicenter trials evaluated 546 adults with active mild to moderate distal UC.<sup>168,169</sup> Oral and rectal corticosteroids, as well as rectal 5-ASA products were prohibited during the course of the trials, but allowed as rescue therapy. Oral 5-ASA products were allowed at doses ≤ 4.8 g/day. Patients were randomized to budesonide rectal foam (n=267) and placebo (n=279). During each trial, patients received budesonide rectal foam 2 mg or placebo twice daily for 2 weeks followed by 2 mg doses once daily for an additional 4 weeks. In each of the 2 trials, the primary endpoint was the proportion of patients who were in remission after 6 weeks of treatment, with remission defined as a decrease or no change in the stool frequency subscore from baseline, a rectal bleeding subscore of 0, and an endoscopy score of 0 or 1. In each trial, a higher proportion of patients in the budesonide rectal foam group than in the placebo group were in remission at Week 6, (38.3% and 44% versus 25.8% and 22.4%, 95% CI) and had a rectal bleeding subscore of 0, (46.6% and 50% versus 28% and 28.6%, 95% CI).

### **mesalamine delayed-release granules (Apriso) versus placebo**

Mesalamine delayed-release granules were evaluated in a double-blind, placebo-controlled trial of patients with UC in remission who took mesalamine DR granules 1.5 g (n=209) or placebo (n=96) once-daily for up to 6 months.<sup>170</sup> The percentage of relapse-free patients at end of treatment was higher with mesalamine than placebo (78.9% versus 58.3%; p<0.001) in the intent-to-treat (ITT) population. Significant differences (p≤0.025) favoring mesalamine were observed for most secondary endpoints including improvement in rectal bleeding, physician's disease activity rating, stool frequency, patients classified as a treatment success, and relapse-free duration. For the mesalamine DR granules-treated group, 31.1% of patients withdrew from the study; UC relapse was the cause for 19.6% (n=41) of patients. For the placebo-treated group, 49% patients (n=47) withdrew from the study; 39.6% of patients (n=38) withdrew due to UC relapse. The incidence of adverse events was similar between groups.

### **mesalamine delayed release (Asacol HD) 4.8 g/day versus mesalamine delayed release (Asacol) 2.4 g/day**

A 6-week, multicenter, randomized, double-blind, active-control study (ASCEND III) was conducted to assess the non-inferiority of mesalamine DR high-dose (Asacol HD) 4.8 g/day to mesalamine DR (Asacol) 2.4 g/day in 772 patients with moderately active UC.<sup>171</sup> The primary endpoint was overall improvement at Week 6 as defined by the Physician's Global Assessment (PGA) (based on clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy) with no worsening in any individual clinical assessment. The primary objective of non-inferiority was met when 70% (273 of 389) of patients who received mesalamine HD 4.8 g/day achieved treatment success at week 6 compared to 66% (251 of 383) of patients receiving mesalamine 2.4 g/day. In addition, 43% of patients receiving the

higher dose of mesalamine achieved clinical remission at Week 6 compared to 35% of patients receiving the lower dose of mesalamine (p=0.4). A therapeutic advantage was observed for those patients who were previously treated with corticosteroids, oral mesalamine, rectal therapies, or multiple UC medications. Both regimens were well tolerated with similar adverse events.

### **mesalamine MMX delayed-release tablets (Lialda) versus placebo**

A randomized, double-blind, parallel-group, placebo-controlled trial was conducted in 280 patients with active, mild to moderate UC over 8 weeks.<sup>172</sup> Patients received mesalamine MMX DR 1.2 g twice daily, 4.8 g once daily, or placebo. The primary efficacy endpoint was percentage of patients in clinical and endoscopic remission after 8 weeks of treatment. Clinical and endoscopic remission at week 8 was achieved by 34.1% and 29.2% of the mesalamine MMX DR 2.4 g/day and 4.8 g/day groups, respectively, versus 12.9% of placebo patients. Mesalamine MMX DR tablets given once or twice daily were well tolerated and compared with placebo, demonstrated efficacy for induction of clinical and endoscopic remission in mild to moderately active UC.

### **mesalamine MMX delayed-release tablets (Lialda) versus mesalamine delayed-release tablets (Asacol)**

An 8-week, double-blind, multicenter trial was conducted in 340 patients with active, mild to moderate UC comparing mesalamine MMX DR 2.4 g/day or 4.8 g/day, mesalamine DR 2.4 g/day given in 3 divided doses, and placebo.<sup>173</sup> The primary endpoint was proportion of patients in clinical and endoscopic remission. Remission was measured by a modified UC disease activity index of  $\leq 1$  with rectal bleeding, stool frequency scores of 0, no mucosal friability, and a  $\geq 1$  point reduction in sigmoidoscopy score from baseline. Patients treated with mesalamine MMX DR experienced significantly greater clinical and endoscopic remission rates by Week 8 versus placebo (2.4 g/day = 40.5%; 4.8 g/day = 41.2%; placebo = 22.1%). The remission rate for mesalamine DR was not significantly greater than placebo (32.6%; p=0.124). All active treatments were well-tolerated.

A 6-month, randomized, double-blind, active-control, multicenter trial was conducted to assess the non-inferiority of once-daily mesalamine MMX (Lialda) 2.4 g/day compared with twice-daily mesalamine DR (Asacol) 1.6 g/day in 826 patients with UC in maintaining endoscopic remission after 6 months.<sup>174</sup> At 6 months, 83.7% and 77.8% of patients receiving mesalamine MMX in the per-protocol and ITT populations, respectively, maintained endoscopic remission compared with 81.5% and 76.9% of patients receiving mesalamine DR (95% CI for difference -3.9%, 8.1% [for the per protocol population, PP]). Time to relapse was not significantly different between the 2 treatment groups (log-rank test, p=0.5116 [PP population]).

### **mesalamine MMX delayed-release tablets (Lialda) low-dose versus mesalamine MMX delayed-release tablets (Lialda) high-dose in pediatrics**

A two-phase, multicenter, randomized, double-blind, parallel group study (n=105; NCT02093663) was conducted to determine the safety and effectiveness of mesalamine MMX (Lialda) in pediatric patients ages 5 to 17 years with mildly to moderately active UC.<sup>175,176</sup> The two phases included an 8-week treatment phase (n=53) and a 26-week maintenance phase (n=87), with an overall population of 105 patients. A total of 27 patients participated in both phases. In each phase, patients were randomized in a 1:1 ratio to receive a low (2.4 g per day maximum) or high (4.8 g per day maximum) weight-based dosage. As there was a very small proportion of patients in the lowest body weight group, safety and

efficacy could not be established in patients weighing < 24 kg. At week 8, approximately 65% of patients in the recommended dosage (high-dose) arm (n=26) achieved the primary outcome, defined as a partial UC Disease Activity Index (UC-DAI)  $\leq 1$  and were eligible to continue in the 26-week treatment phase along with other eligible patients with a UC-DAI score of  $\leq 2$  with an endoscopic subscore of 0 or 1. A total of 87 patients were enrolled in the 26-week maintenance phase. The primary outcome was the same as for the 8-week phase and was reached by 55% of the 42 patients in the recommended dosage (low-dose) arm. The higher dosage was not found to be more effective than the recommended dose amongst the patients in the maintenance phase. Therefore, the higher weight-based dose is not labeled for use beyond 8 weeks.

### **olsalazine (Dipentum) versus sulfasalazine (Azulfidine)**

A randomized, double-blind, 6-month study compared 3 doses of olsalazine (0.5 g, 1.25 g, and 2 g daily) and sulfasalazine 2 g daily for maintenance of remission in 162 patients with UC.<sup>177</sup> Using intention-to-treat analysis, failure rates of the different treatment groups were not significantly different (36%, 49%, and 24% for 0.5 g, 1.25g, and 2 g olsalazine daily and 32% for 2 g sulfasalazine daily). Olsalazine and sulfasalazine showed a tendency towards lower failure rates in extended disease (28%) than in distal disease (44%). Withdrawal rate due to adverse effects was 4%, with the most frequent single event being diarrhea, which occurred only in patients treated with olsalazine (2.5%, 5.2%, and 11.7% for daily olsalazine doses of 0.5 g, 1.25, and 2 g, respectively).

A randomized, double-blind trial compared the relapse-preventing effects of olsalazine and sulfasalazine in patients with UC over 12 months.<sup>178</sup> A total of 227 patients received either olsalazine 500 mg twice daily or sulfasalazine 1 g twice daily. A total of 197 patients completed the trial. Relapse rate after 12 months were found to be comparable; 46.9% in the olsalazine group versus 42.4% in the sulfasalazine group (95% CI, -9 to 18). Equal numbers of patients in each group withdrew from the trial because of adverse effects.

### **olsalazine (Dipentum) versus sulfasalazine (Azulfidine) in pediatrics**

Safety and efficacy of olsalazine (Dipentum) were compared to sulfasalazine over 3 months in a multicenter, randomized, double-blind study of 56 children with mild to moderate UC.<sup>179</sup> Twenty-eight children received 30 mg/kg/day of olsalazine (maximum of 2 g/day) and 28 received 60 mg/kg/day of sulfasalazine (maximum of 4 g/day). After 3 months, 39% of olsalazine-treated patients were asymptomatic or clinically improved, compared to 79% of sulfasalazine-treated patients (p=0.006). In addition, 10 of 28 patients on olsalazine versus 1 on sulfasalazine required prednisone because of lack of response or worsening of colitis (p=0.005). The dose of olsalazine used in the trial was equivalent to a standard dose of sulfasalazine, but fewer patients on olsalazine improved and a greater number had progression of symptoms when compared to sulfasalazine. Adverse effects were frequent in both groups; a clinically significant difference was not detected.

## **META-ANALYSIS**

A 2020 meta-analysis provided an update of a prior Cochrane review evaluating oral 5-aminosalicylic acid (5-ASA) for induction of remission in UC.<sup>180</sup> A total of 54 studies evaluating 9,612 individuals were selected for inclusion; studies were randomized controlled trials (RCTs) assessing adults with active UC. Oral 5-ASA could have been compared to placebo, sulfasalazine, or other 5-ASA formulations. Overall, the majority of studies were determined to have a low risk of bias. Across 11 studies assessing 2,387

participants, 71% of individuals who received 5-ASA did not enter clinical remission compared to 83% of those who received placebo (relative risk [RR], 0.86; 95% CI, 0.82 to 0.89; high-certainty evidence). A dose-response trend was seen with 5-ASA. In terms of 5-ASA compared to sulfasalazine, no difference was found in clinical remission rates with 54% of 5-ASA patients failing to enter remission versus 58% of sulfasalazine patients (RR, 0.9; 95% CI, 0.77 to 1.04) based on 8 studies (moderate-certainty evidence). Additionally, no difference in remission rates was found when once-daily dosing was compared to conventional dosing for 5-ASA. Furthermore, no difference in efficacy was observed among various 5-ASA formulations (moderate-certainty evidence), and no difference in the proportion of adverse events (AEs) and serious adverse events (SAEs) was found between 5-ASA and placebo, once-daily and conventionally-dosed 5-ASA, and 5-ASA and comparator 5-ASA formulations. Common AEs observed across the studies were flatulence, abdominal pain, nausea, diarrhea, headache, and worsening UC. In terms of the tolerability of sulfasalazine compared to 5-ASA, across 12 studies, 29% of sulfasalazine-treated patients had an AE compared to 15% of 5-ASA participants (RR 0.48; 95% CI, 0.36 to 0.63; moderate-certainty evidence). Authors concluded 5-ASA is superior to placebo (high-certainty evidence) and not more effective than sulfasalazine (moderate-certainty evidence). Furthermore, data suggests 5-ASA dosed once daily is likely as effective as conventionally-dosed 5-ASA (high-certainty evidence). Lastly, there are few, if any, differences in efficacy or safety between the various 5-ASA formulations for inducing remission.

A 2020 meta-analysis provided an update of a prior Cochrane review evaluating oral 5-ASA for maintenance of remission in UC.<sup>181</sup> A total of 44 studies evaluating 9,967 patients was identified. Studies included were RCTs with a minimum treatment duration of 6 months that evaluated oral 5-ASA therapy to placebo, sulfasalazine, or other 5-ASA formulations in patients with quiescent UC. Across 8 studies (n=1,555), 5-ASA was found to be more effective than placebo for maintenance of remission (clinical or endoscopic) as approximately 37% of 5-ASA patients experienced a relapse at 6 to 12 months compared to 55% of patients who received placebo (RR 0.68; 95% CI, 0.61 to 0.76; high-certainty evidence). Based on 12 studies (n=1,655), it was determined that sulfasalazine was more effective than 5-ASA for maintenance of remission with approximately 48% of 5-ASA-treated patients experiencing a relapse at 6 to 18 months compared with 43% of sulfasalazine-treated patients (RR 1.14; 95% CI, 1.03 to 1.27; high-certainty evidence). Although adherence to study medication and SAEs were not detailed for this comparison, it was concluded there was likely little to no difference in AEs at 6 to 12 months (RR 1.07, 95% CI 0.82 to 1.40; moderate-certainty evidence). Differences in the efficacy of different 5-ASA formulations were minimal or absent based on 44% of individuals in the 5-ASA group relapsing at 6 to 18 months compared with 41% of those in 5-ASA comparator group (RR 1.08; 95% CI, 0.91 to 1.28; low-certainty evidence). Common AEs (flatulence, abdominal pain, nausea, diarrhea, headache, and dyspepsia) are likely similar between 5-ASA and placebo as well as 5-ASA and sulfasalazine. Authors concluded that 5-ASA is superior to placebo for maintenance therapy in UC (high-certainty evidence), and that 5-ASA is inferior to sulfasalazine (high-certainty evidence). Lastly, findings suggest oral 5-ASA once daily has comparable efficacy and safety to conventional dosing for maintenance of remission. An earlier meta-analysis resulted in similar conclusions.<sup>182</sup>

## SUMMARY

Aminosalicylates remain first-line treatment options for mild to moderate active ulcerative colitis (UC); 90% of patients are treated with this class shortly after disease diagnosis. Mesalamine agents currently are available in oral and rectal formulations. The relative tolerability and compliance must be

considered in evaluation of the oral mesalamine preparations. Pill burden might also be a factor in treatment decision-making.

Mesalamine controlled-release (Pentasa) is dosed 4 times a day using 8 capsules and mesalamine delayed-release (Delzicol) is dosed 3 times a day using 6 capsules. Another formulation of mesalamine delayed-release (Asacol HD) is available at a higher strength that also allows for 3 times daily dosing using 6 tablets in total. One Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Delzicol 400 mg capsules; therefore, substitution should not occur. Mesalamine MMX delayed-release (Lialda) and mesalamine ER capsules (Apriso) are dosed once daily using no more than 4 tablets or capsules.

Balsalazide (Colзал) is indicated for UC treatment, while olsalazine (Dipentum) is indicated for UC maintenance. Olsalazine has a low pill burden of 2 capsules twice daily, however the tolerability of olsalazine is often limited by a high rate of secretory diarrhea.

The adverse effect profile for sulfasalazine is less favorable than newer agents especially at higher doses. Patients with disease affecting the distal portion of the colon should use a rectal preparation either alone or in combination with oral therapy. Enemas and suppositories may provide quicker response time as well as less frequent dosing compared to oral therapy. Rectally administered mesalamine (generic, Rowasa enemas, sfRowasa enemas, Canasa suppositories) has a specific role as a non-oral treatment of distal UC, proctosigmoiditis, and proctitis. Tolerability of rectal formulations is variable based on an individual patient's ability to retain the drug preparation for the allotted time. The sulfite-free mesalamine enema (sfRowasa) was FDA-approved as a formulation revision with a new trade name. It is proposed to cause less bowel irritation and to be safe for use by patients with sulfite allergy; however, this has yet to be demonstrated clinically.

Extended-release budesonide (Uceris) oral and rectal foam offer alternatives for induction of remission in mild to moderate UC, but they, along with systemic corticosteroids, should not be used in maintenance of remission.

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