



Ulcerative Colitis Agents

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Oral Prodrug Forms			
balsalazide (Colazal®) ¹	Salix	Mild to moderately active ulcerative colitis (UC) in patients 5 years of age and older.	--
balsalazide (Giazo®) ²	Salix	Mild to moderately active ulcerative colitis in male patients 18 years of age and older.	--
olsalazine (Dipentum®) ³	Alaven	--	Maintenance of remission of UC in patients intolerant of sulfasalazine
sulfasalazine (Azulfidine®, Azulfidine EN-tabs®) ^{4,5}	generic	Mild to moderately active UC Adjunctive therapy in severe UC	Maintenance of remission of UC
<p>Other: Enteric-coated tablets are indicated in patients with UC who cannot take uncoated sulfasalazine tablets because of 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.</p>			
Oral Delayed-Release Forms			
mesalamine delayed release tablets (Asacol®) ⁶	Procter & Gamble	Mild to moderately active UC	Maintenance of remission of UC
mesalamine delayed release capsules (Delzicol®) ⁷	Warner Chilcott	Mild to moderately active UC	Maintenance of remission of UC
mesalamine delayed-release tablets (Asacol® HD) ⁸	Procter & Gamble	Moderately active UC	--
mesalamine MMX delayed release tablets (Lialda™) ⁹	Shire US	Mild to moderately active UC	Maintenance of remission of UC
mesalamine extended release capsules (Pentasa®) ¹⁰	Shire US	Mild to moderately active UC	--
mesalamine extended-release capsules (Apriso™) ¹¹	Salix	--	Maintenance of remission of UC in adults

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Rectal Forms			
mesalamine enemas (Rowasa®)	generic	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine enemas sulfite-free (sfRowasa®)	Alaven Pharm	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine suppositories (Canasa®)	Axcan Scandipharm	Active ulcerative proctitis	--
Oral Corticosteroids			
budesonide extended-release tablets (Uceris®) ¹²	Santarus	Induction of remission in active, mild to moderate UC	--

OVERVIEW

Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colon and rectum. The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in multiple mucosal ulcerations and crypt abscesses. The lesions are contiguous, typically extending retrograde from the rectum, involving the descending, transverse, or the entire colon. The principal goal of treatment for UC is inducing, then maintaining, remission of the disease.

UC affects approximately 500,000 persons in the United States with an incidence of eight to twelve per 100,000 population per year.¹³ The disease accounts for 250 million annual physician visits; 30,000 hospitalizations; and a loss of over one million workdays per year. The onset of UC is most common between 15 and 40 years of age, with a second peak between 50 and 80 years of age.

The predominant symptom of UC is diarrhea which is usually associated with blood in the stool. Bowel movements are frequent but small in volume as a result of rectal inflammation. Other symptoms include 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. Elderly patients often complain of constipation rather than diarrhea because rectal spasm prevents passage of stool. The initial attack of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea. Ulcerative colitis can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to pancolitis. Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course.¹⁴

Aminosaliclates remain first-line treatment options for mild to moderate active UC.¹⁵ The mesalamine agents currently are available in oral and rectal formulations. The rectal products achieve high luminal concentrations of the active component, 5-aminosalicylic acid (5-ASA, mesalamine), while minimizing adverse events due to systemic absorption. Several aminosaliclates are available and differ only in mode of distribution throughout the small intestine and colon. **Second-line therapy with a course of oral steroids is indicated in patients with mild to moderate disease that does not respond to oral and rectal mesalamine agents or in patients with moderate to severe disease.**¹⁶

For active ulcerative proctitis, an effective and rapid-acting approach is nightly administration of mesalamine retention enemas or suppositories, often supplemented with an oral aminosalicylate. Corticosteroid enemas can also be used. Another approach to proctitis is administration of an oral aminosalicylate alone, although therapeutic response may not be evident for three to four weeks.¹⁷

In 2007, the American Academy of Family Physicians (AAFP) released guidelines for the diagnosis and treatment of UC.¹⁸ The guidelines 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. According to the AAFP guidelines, 5-ASA (mesalamine) via suppository or enema is 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. In patients with greater colonic involvement, first-line therapy should include oral mesalamine and oral corticosteroids to maintain remission. To prevent relapse of the disease, patients with UC may be given nonpathogenic *Escherichia coli* instead of 5-ASA. Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with azathioprine (Imuran) or infliximab (Remicade®). For patients who fail to improve with the maximal dosage of 5-ASA compounds or who cannot tolerate the side effects, oral steroid therapy may be used. Prednisone is given in dosages of 40 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. Long-term oral steroid use is not recommended for chronic maintenance due to significant side effects.

The 2010 Practice guidelines of the American College of Gastroenterology state differences in treatment based on disease severity.¹⁹ The recommendations for maintenance and remission in distal disease include mesalamine suppositories in patients with proctitis and mesalamine enemas in patients with distal colitis (even when dosed as infrequently as every third night). Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission. The combination of oral and rectal mesalamine is more effective than either one alone. Patients with active disease (mild to moderate extensive colitis) should begin therapy with oral sulfasalazine or an alternate aminosalicylate.

In patients with severe or refractory UC symptoms, oral corticosteroids are indicated. Corticosteroids, while highly efficacious in short term use, have numerous adverse effects, especially in the elderly, which preclude long-term use.²⁰ Patients who respond to oral prednisone and can be fully withdrawn from the drug should be maintained on an aminosalicylate. For patients with corticosteroid-dependent or corticosteroid-refractory disease, immunosuppression with azathioprine or mercaptopurine may prevent colectomy.²¹ Infliximab, a Tumor Necrosis Factor Inhibitor (TNF-inhibitor), is approved for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderate to severe active UC who fail conventional therapy. Aminosalicylates are the focus of this review.

PHARMACOLOGY

The first oral aminosalicylate developed, sulfasalazine, consists of a sulfapyridine carrier moiety linked to 5-ASA via an azo bond.²² Colonic bacteria cleave the azo bond, converting sulfasalazine into sulfapyridine and 5-ASA moieties.²³ While the sulfapyridine is absorbed and excreted in the urine, the 5-ASA component stays in the colon and is excreted in the feces. Although the specific mechanism is unknown, the intraluminal activity of 5-ASA produces a local therapeutic effect.^{24,25} Mucosal production of arachidonic acid metabolites, through cyclooxygenase and lipoxygenase pathways, is

increased in patients with chronic inflammatory bowel disease. 5-ASA may decrease inflammation by blocking production of arachidonic acid metabolites in the colon.^{26,27}

Newer oral agents were developed to enhance 5-ASA delivery to the colon and reduce the incidence of adverse events.²⁸ The formulations fall into three categories: azo-bonded prodrug formulations (Colazal, **Giazo**, Dipentum), delayed-release formulations achieved by pH shift (Apriso, Asacol, Asacol HD, and Lialda) or controlled-release formulations (Pentasa). The azo-bonded prodrugs are similar to sulfasalazine, and colonic bacteria are required to cleave the azo bond and release the active 5-ASA moiety.^{29,30} Effectiveness of delayed and controlled-release formulations may be variable because release of mesalamine is pH-dependent. As a result, early release increases absorption of 5-ASA in the proximal small intestine, increasing systemic exposure to 5-ASA and possible nephrotoxicity.³¹ Apriso capsules have the Intellicor extended release delivery technology that combines an enteric pH-dependent coating giving a delayed release starting at a pH of 6.0 followed by a polymer matrix core that provides for extended release.³² Asacol and Asacol HD tablets are coated with a pH-sensitive acrylic polymer that delays the release of 5-ASA. Lialda uses MMX technology, a pH-dependent gastro-resistant coating, to delay the release of 5-ASA from the tablet core to the colon. Pentasa uses a water gradient to release microspheres containing 5-ASA from the capsule.

In March 2012, the FDA issued a draft guidance recommending against use of two specific phthalates, dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP), as excipients due to developmental and reproductive toxicants in laboratory animals and potential for being endocrine disrupting, and affecting reproductive and developmental outcomes in humans.³³ These agents are often used as plasticizers in enteric and delayed release coatings of drug products, including select mesalamine DR products (Asacol and Asacol HD). The draft guidance recommended that manufacturers reformulate products containing these excipients. A final guidance was issued in December 2012.³⁴ Mesalamine DR (Delzicol) has been formulated without DBP but 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 the treatment of up to 20 cm of distal colon. Mesalamine (or corticosteroid) retention enemas, which distribute drug to the left colon, can be used for active disease involving up to 60 cm of distal colon.³⁵ A sulfite-free formulation of mesalamine enema (sfRowasa) has been FDA-approved.

Steroids, such as budesonide ER (Uceris), may suppress autoimmune and inflammatory responses in UC. Budesonide has a high topical glucocorticosteroid activity and a substantial first-pass elimination. Uceris is a delayed and extended-release tablet, which breaks down at pH \geq 7.0. Uceris uses MMX technology.

PHARMACOKINETICS ^{36,37,38,39,40,41,42,43,44,45,46,47,48,49,50}

All **aminosalicylate** oral products are designed to release 5-ASA for action in the intestine so 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 elimination half-life of 5-ASA can range from two to 15 hours due to the different formulations of the drugs.

Drug	Delivery Mechanism	Bioavailability (%)
Oral Prodrug Forms		
balsalazide (Colazal, Giazo)	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
Oral Delayed-Release Forms		
mesalamine delayed release tablets (Asacol)	Acrylic-based resin coating delays 5-ASA release until tablet reaches the terminal ileum and beyond; pH dependent release at pH \geq 7	28
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, Eudragit S (methacrylic acid copolymer type B, NF), which delays 5-ASA release until capsule reaches the terminal ileum and beyond; pH dependent release at \geq pH 7	28
Oral Delayed-Release Forms		
mesalamine MMX tablets (Lialda)	pH-dependent gastro-resistant coating that delays release of 5-ASA until the tablet reaches the colon; pH dependent release at pH \geq 7	21-22
mesalamine capsules (Pentasa)	Ethylcellulose-coated, controlled release formulation releases 5-ASA throughout the intestinal tract	20-30
mesalamine ER capsules (Apriso)	Intellicor extended-release delivery technology that combines an enteric pH-dependent coating which provides for a delayed release starting at a pH of 6.0 with a polymer matrix core that enables extended release	21-44

Pharmacokinetics (continued)

Drug	Delivery Mechanism	Bioavailability (%)
Rectal Forms		
mesalamine enemas (Rowasa, sfRowasa)	Rectal administration	10-30
mesalamine suppositories (Canasa)	Rectal administration	variable
Oral Corticosteroids		
budesonide ER tablets (Uceris) ⁵¹	pH dependent enteric coated delayed release tablets with a polymer coating that dissolves at pH \geq 7.0 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 one Asacol HD 800 mg tablets.

CONTRAINDICATIONS/WARNINGS^{52,53,54,55,56,57,58,59,60,61,62}

Aminosalicylates are contraindicated in patients with salicylate hypersensitivity. 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 Uceris.

Deaths associated with administration of sulfasalazine have been reported. Deaths occurred from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, 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 done 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.

Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Renal impairment 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. Patients with pyloric stenosis may have prolonged gastric retention of oral mesalamine and balsalazide which could delay the release of drug in the colon. There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. 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.

Mesalamine enemas (Rowasa Rectal Suspension Enema) contain 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.

Dibutyl phthalate (DBP) is an inactive ingredient in the enteric coating of Asacol and Asacol HD brand (mesalamine) tablets. In animal studies at doses Asacol HD >80 times and Asacol >190 times the human dose based on body surface area, maternal DBP was associated with external and skeletal malformations and adverse effects on the male reproductive system. Asacol and Asacol HD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 use in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, 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^{63,64,65,66,67,68,69,70,71,72}

Antacids: Mesalamine extended-release capsules (Apriso) depend on pH for dissolution of the coating of the granules so concomitant use with antacids should not occur.

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

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

Phenytoin: Sulfasalazine can displace highly protein-bound drugs such as phenytoin.

Warfarin: Salicylates may displace warfarin from protein binding sites leading to hypoprothrombinemia. This dose-related interaction has been reported with olsalazine and sulfasalazine.

Dissolution of the coating of budesonide ER (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., PPIs, H₂-blockers and antacids). Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4) caused an eight-fold increase in the systemic exposure to oral budesonide ER. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, or 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 two fold. Consequently ingestion of grapefruit or grapefruit juice should be avoided with budesonide ER administration.

ADVERSE EFFECTS^{73,74,75,76,77,78,79,80,81,82,83,84}

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
Oral Prodrug Forms							
balsalazide (Colazal)	6-13 (3)	5-9 (3)	2-6 (0)	8-15	4-5	nr	4-10
balsalazide (Giazo)	nr	3.7 (0)	nr	nr	nr	nr	nr
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
Oral Delayed-Release Forms							
mesalamine tablets (Asacol)*	18 (14)	7 (9)	6 (8)	35 (36)	13 (15)	6 (3)	5 (2)
mesalamine delayed-release tablets (Asacol HD)	2.3	1.7	rare	4.7	2.8	reported	1.4

Adverse Effects (continued)

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
Oral Delayed-Release Forms (continued)							
mesalamine MMX tablets (Lialda)	<1	<1	reported	3.4-5.6 (0.6)	nr	<1	<1
mesalamine 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
Rectal Forms							
mesalamine enemas (Rowasa)	8.1 (7.8)	2.1 (3.1)	3.2 (0)	6.5 (12.5)	5.8 (9.4)	2.8 (3.1)	<1
mesalamine enemas sulfite-free (sfRowasa)							
mesalamine suppositories (Canasa)	5.2	3.1	1.2 (0)	14.4	3.1	1.2 (0)	<1
Oral Corticosteroids							
budesonide ER tablets (Uceris) ⁸⁵	3.9 (1.9)	nr	nr	11.4 (10.5)	5.1 (4.3)	nr	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.

Clinical tolerance of three aminosalicylate preparations [mesalamine (Asacol), olsalazine (Dipentum), and balsalazide] was assessed in a consecutive series of 43 patients with inflammatory bowel disease intolerant to sulfasalazine.⁸⁶ Ninety-one percent of patients were able to tolerate at least one of the three preparations. Clinical tolerance of mesalamine (63 percent), olsalazine (70 percent), and balsalazide (70 percent) was similar. The most common adverse effects associated with the preparations were gastrointestinal in nature; diarrhea was a problem in five patients during treatment with olsalazine and three each while on mesalamine and balsalazide. Allergic reactions to aminosalicylates were uncommon; of ten patients with rash following sulfasalazine, only one 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 one of the four aminosalicylates, and adverse effects of sulfasalazine are multifactorial in etiology. Some adverse effects are due to the parent molecule, and some to one of its two metabolites, 5-ASA and sulfapyridine.

Renal impairment and injury including nephropathy, acute and chronic interstitial nephritis, and rarely, renal failure, have been reported in patients taking products that contain or are converted to mesalamine. In addition, 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. Patients with pyloric stenosis may have prolonged gastric retention of Asacol HD tablets, which could delay release of mesalamine in the colon. Lastly, there have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine.

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 III clinical trials, there were no clinically significant differences in glucocorticoid-related adverse events between budesonide ER (Uceris) 9 mg and placebo at eight weeks.⁸⁷

SPECIAL POPULATIONS^{88,89,90,91,92,93,94,95,96,97,98,99}

Pediatrics

Safety and efficacy of olsalazine (Dipentum) were compared to sulfasalazine over three months in a multicenter, randomized, double-blind study of 56 children with mild to moderate UC.¹⁰⁰ 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 three months, 39 percent of olsalazine-treated patients were asymptomatic or clinically improved, compared to 79 percent of sulfasalazine-treated patients (p=0.006). In addition, 10 of 28 patients on olsalazine versus one 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. Safety and effectiveness of olsalazine in a pediatric population have not been established.

Sulfasalazine is approved for use in patients six years of age and older. Balsalazide 750 mg, (Colazal), is approved for use in patients five years of age and older, whereas balsalazide 1 gm (Giazo) is only approved in male patients 18 years and older. Colazal capsules may be opened and sprinkled on applesauce, then chewed or swallowed immediately. Other products have not been sufficiently studied in pediatric populations.

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

Geriatrics

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, e.g., neutropenia and pancytopenia, in patients who were 65 years or older who were taking mesalamine-containing products. Caution should be taken to closely monitor blood cell counts during therapy.

Clinical studies of budesonide ER (Uceris) did not include sufficient subjects aged 65 and over to determine whether they respond differently from 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.

Pregnancy

Olsalazine (Dipentum), mesalamine (Asacol and Asacol HD only), and budesonide ER (Uceris) are Pregnancy Category C. All Asacol and Asacol HD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Balsalazide (Colazal, Giazo) and mesalamine (Delzicol) are Pregnancy Category B.

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.

Hepatic Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism with budesonide ER (Uceris).

DOSAGES^{101,102,103,104,105,106,107,108,109,110,111,112,113,114,115}

Drug	Adults	Pediatrics	Availability
Oral Prodrug Forms			
balsalazide (Colazal)	2.25 g (three 750mg capsules) three times daily for eight to twelve weeks (Total Daily Dose: 6.75 g)	Children five to 17 yrs 2.25 g (three 750mg capsules) three times daily for eight weeks OR 750 mg (1 capsule) three times daily for eight weeks*	750 mg capsule
balsalazide (Giazo)	3.3 g (three 1.1 g tablets) two times daily with or without food for up to eight weeks (Total Daily Dose: 6.6 g)		1.1 g tablet
olsalazine (Dipentum)	0.5 g twice daily	--	250 mg capsule
sulfasalazine	Treatment: three to four grams daily in evenly divided doses with dosage intervals not exceeding eight hours Maintenance: two grams daily	Children six years and older Treatment: 40 to 60 mg/kg/day divided into three to six doses Maintenance: 30 mg/kg/day divided into four doses	500 mg tablet 500 mg enteric coated delayed-release tablet

Dosages (continued)

Drug	Adults	Pediatrics	Availability
Oral Delayed-Release Forms			
mesalamine tablets (Asacol)	Initial dose: 0.8 g three times daily for six weeks Maintenance dose: 1.6 g per day in divided doses for six months	--	400 mg delayed-release tablet
mesalamine delayed-release tablets (Asacol HD)	1.6 g three times daily with or without food for six weeks (Total daily dose of 4.8 g)	--	800 mg delayed-release tablet
mesalamine delayed release capsules (Delzicol)	Initial dose: 0.8 g three times daily for six weeks; 2.4 g total Maintenance dose: 1.6 g per day in divided doses for six months Dose at least 1 hour before a meal or 2 hours after a meal.**	--	400 mg delayed-release capsule
mesalamine MMX tablets (Lialda)	2.4 g or 4.8 g (two to four tablets) once daily with a meal for up to eight weeks † Maintenance of remission: 2.4 g (two tablets) once daily with a meal †	--	1.2 g delayed-release tablet
mesalamine capsules (Pentasa)	1 g four times a day for up to eight weeks	--	250 mg controlled-release capsules
mesalamine ER capsules (Apriso)	1.5 g once daily in the morning with or without food	--	0.375 mg extended-release capsules
Rectal Forms			
mesalamine enemas (Rowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of eight hours) for three to six weeks	--	4 g/60 mL enema (7, 14 and 28 unit packages)
mesalamine enemas sulfite-free (sfRowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of eight hours) for three to six weeks	--	4 g/60 mL enema (7, 14 and 28 unit packages)
mesalamine suppositories (Canasa)	1 g daily at bedtime (and retained for a minimum of one to three hours) for three to six weeks	--	1,000 mg suppositories
Oral Corticosteroids			
budesonide ER tablets (Uceris) ¹¹⁶	9 mg orally once daily in the morning with or without food for up to 8 weeks.	--	9 mg enteric coated delayed and extended release tablets

* Balsalazide capsules may be opened and sprinkled on applesauce; contents may be chewed.

† Safety and efficacy of mesalamine MMX extended-release (Lialda) past eight weeks of treatment of UC have not been established. The duration of mesalamine Intellicor extended-release (Apriso) use for maintaining remission of UC beyond six months has not been evaluated.

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

** Mesalamine DR (Delzicol): swallow whole, do not chew, crush or break. Delzicol has been formulated without dibutyl phthalate (DBP).

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 percent 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.¹¹⁷

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 delayed-release granules 1.5 g (n=209) or placebo (n=96) once-daily for up to six months.¹¹⁸ The percentage of relapse-free patients at month end of treatment was higher with mesalamine than placebo (78.9 versus 58.3 percent, $p < 0.001$) in the intent-to-treat population. Significant differences ($p \leq 0.025$) 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 delay-release granules-treated group, 31.1 percent of patients withdrew from the study; UC relapse was the cause for 19.6 percent (n=41) of patients. For the placebo-treated group, 49 percent patients (n=47) withdrew from the study; 39.6 percent of patients (n=38) withdrew due to UC relapse. The incidence of adverse events was similar between groups. This study was sponsored by the manufacturer of Apriso, Salix Pharmaceuticals.

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

Delayed-release oral mesalamine 2.4 g/day to 4.8 g/day has been shown to be effective in treating mild to moderately active UC; but it is unknown whether an initial dose of 4.8 g/day is more effective than 2.4 g/day in patients with mild to moderately active UC and in a subgroup with moderate disease.¹¹⁹ A six-week, multicenter, randomized, double-blind, controlled trial assessing the safety and clinical efficacy of a new dose (ASCEND I) of medication randomly assigned 301 adults with mild to

moderate active UC to delayed-release oral mesalamine 2.4 g/day (400 mg; n=154) or 4.8 g/day (800 mg; n=147). Primary efficacy endpoint was overall improvement defined as complete remission or response to therapy from baseline to week six. Primary safety end points were adverse events and laboratory evaluations. Treatment success was not statistically different between the groups at week six; 51 percent of the group who received 2.4 g/day and 56 percent of the group who received 4.8 g/day reached the efficacy endpoint (p=0.441). In the moderate disease subgroup, the higher initial dose was more effective (57 versus 72 percent in the 2.4 versus 4.8 g/day groups, respectively; p=0.0384). Both regimens were well tolerated. In conclusion, the initial 4.8 g/day dose may be better reserved for patients with moderate disease.

Treatment success with any product is often dose-related, as seen in other studies such as ASCEND II, where overall improvement was significantly more likely with higher doses of mesalamine.¹²⁰

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

A six-week, multicenter, randomized, double-blind, active-control study (ASCEND III) was conducted to assess the noninferiority of mesalamine delayed release high dose (Asacol HD) 4.8 g/day to mesalamine delayed release (Asacol) 2.4 g/day in 772 patients with moderately active UC.¹²¹ The primary endpoint was overall improvement at week six as defined by the Physician's Global Assessment (based on clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy) with no worsening in any individual clinical assessment. The primary objective of noninferiority was met when 70 percent (273 of 389) of patients who received mesalamine 4.8 g/day achieved treatment success at week six compared to 66 percent (251 of 383) of patients receiving mesalamine 2.4 g/day. In addition, 43 percent of patients receiving the higher dose of mesalamine achieved clinical remission at week six compared to 35 percent 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.

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

A double-blind study compared the effectiveness of balsalazide and mesalamine delayed-release in the treatment of 101 patients with active moderate to severe UC.¹²² Patients were randomized to receive balsalazide 6.75 g/day or mesalamine delayed-release 2.4 g/day for 12 weeks. After two, four, and 12 weeks, symptom control was greater in the balsalazide group. Remission rate after 12 weeks of therapy was 62 percent with balsalazide and 37 percent with mesalamine delayed-release. Median time to first day of complete relief of symptoms was ten days for the balsalazide group and 25 days for the mesalamine delayed-release group. Adverse effects occurred in 48 percent of patients treated with balsalazide and 71 percent of those treated with mesalamine delayed-release.

A randomized, double-blind, double-dummy, parallel-group, dose-response study was performed comparing balsalazide 2.25 or 6.75 g daily and delayed-release mesalamine 2.4 g daily.¹²³ Medication was administered for eight weeks to 154 patients with active, mild to moderate UC, the majority of who 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 delayed-release was more rapid onset of action as determined by a better two-week sigmoidoscopic score for patients treated with

balsalazide (55 versus 29 percent; $p=0.006$). Balsalazide 6.75 g daily was well tolerated, and the safety profile did not differ significantly from either balsalazide 2.25 g daily or mesalamine delayed-release 2.4 g daily.

A total of 173 patients with active, mild to moderate UC were randomized to eight weeks of double-blind treatment with balsalazide 2.25 g or mesalamine 0.8 g, each given three times daily.¹²⁴ Overall, 46 percent of balsalazide-treated and 44 percent 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 percent of balsalazide- and 64 percent of mesalamine-treated patients reported at least one 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 two Asacol products.¹²⁵

balsalazide (Giazo) versus placebo

A double-blind, placebo-controlled, multicenter trial was conducted in 250 male and female adult patients with mild to moderate active ulcerative colitis.¹²⁶ Patients were randomized 2:1 to receive eight weeks of treatment with either balsalazide 3.3 g twice daily or placebo. Disease activity was assessed using a modified Mayo Disease Activity Index (MMDAI). The primary efficacy endpoint was the proportion of patients that achieved clinical improvement and improvement in the rectal bleeding subscale of the MMDAI at the end of eight weeks of treatment. Clinical Improvement was defined as having both greater than or equal to a three point improvement from baseline in the MMDAI score and greater than or equal to a one point improvement from baseline in the rectal bleeding sub score. At total of 55 percent of patients had clinical improvement with balsalazide compared to 40 percent on placebo, ($p=0.0237$). This difference in clinical improvement was completely due to improvement in males (57 percent improved with balsalazide versus 20 percent with placebo). There was no difference in the percentage of females with clinical improvement (54 percent versus 58 percent with balsalazide versus placebo, respectively).

olsalazine (Dipentum) versus sulfasalazine (Azulfidine)

A randomized, double-blind, six-month study compared three doses of olsalazine (0.5, 1.25, and 2 g daily) and sulfasalazine 2 g daily for maintenance of remission in 162 patients with UC.¹²⁷ Using intention-to-treat analysis, failure rates of the different treatment groups were not significantly different (36, 49, and 24 percent for 0.5, 1.25 and 2 g olsalazine daily and 32 percent for 2 g sulfasalazine daily). Olsalazine and sulfasalazine showed a tendency towards lower failure rates in extended disease (28 percent) than in distal disease (44 percent). Withdrawal rate due to adverse effects was four percent with the most frequent single event being diarrhea, which occurred only in

patients treated with olsalazine (2.5, 5.2, and 11.7 percent for daily olsalazine doses of 0.5, 1.25, and 2.0 g, respectively).

A randomized, double-blind trial compared the relapse-preventing effects of olsalazine and sulfasalazine in patients with UC over 12 months.¹²⁸ 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 in the olsalazine group was 46.9 percent versus 42.4 percent in the sulfasalazine group (95% confidence interval (CI), -9 to 18 percent). Equal numbers of patients in each group withdrew from the trial because of adverse effects.

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 eight weeks.¹²⁹ Patients received mesalamine MMX delayed-release 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 eight weeks of treatment. Clinical and endoscopic remission at week eight was achieved by 34.1 percent and 29.2 percent of the mesalamine MMX delayed-release 2.4 g/day and 4.8 g/day groups, respectively, versus 12.9 percent of placebo patients. Mesalamine MMX delayed-release 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 eight-week, double-blind, multicenter trial was conducted in 340 patients with active, mild to moderate UC comparing mesalamine MMX delayed-release 2.4 g/day or 4.8 g/day, mesalamine delayed-release 2.4 g/day given in three divided doses, or placebo.¹³⁰ The primary endpoint was proportion of patients in clinical and endoscopic remission. Remission was measured by a modified UC disease activity index of less than or equal to one with rectal bleeding, stool frequency scores of zero, no mucosal friability, and a greater than or equal to one point reduction in sigmoidoscopy score from baseline. Patients treated with mesalamine MMX delayed-release experienced significantly greater clinical and endoscopic remission rates by week eight versus placebo (2.4 g/day = 40.5 percent; 4.8 g/day = 41.2 percent; placebo = 22.1 percent). The remission rate for mesalamine delayed-release was not significantly greater than placebo (32.6 percent; $p=0.124$). All active treatments were well-tolerated.

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 ≥ 4 and ≤ 10 and histology consistent with active UC.¹³¹ 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 eight weeks and remission was defined as a UCDAI score of ≤ 1 , with sub scores of zero for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score. At the end of eight weeks 17.4 percent in the budesonide ER 9 mg group, 8.3 percent in the budesonide ER 6 mg group, 12.6 percent in the budesonide 9 mg group, and 4.5 percent of placebo,

were in remission. The difference in remission rate for budesonide ER 9 mg versus placebo was 12.9 percent (95% CI, 4.6-21.3, $p < 0.025$ on a Chi-square test [$\alpha = 0.025$]).

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.^{132,133} Budesonide ER 9 mg and budesonide ER 6 mg (not approved in the US) was compared with mesalamine DR 2.4 g (as reference), and to placebo. The primary endpoint was induction of remission after eight weeks. Remission was defined as a UCDAI score of ≤ 1 , with sub scores of zero for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score. At the end of 8 weeks 17.9 percent of patients administered budesonide ER 9 mg, 13.2 percent in the budesonide ER 6 mg arm, 12.1 percent in the mesalamine DR 2.4 g arm, and 7.4 percent of placebo, were in remission. The difference in remission rate for budesonide ER 9 mg compared to placebo was 10.4 percent (95% CI, 2.2-18.7, $p < 0.025$ on a Chi-square test [$\alpha = 0.025$]). Adverse events occurred at similar rates among groups.

SUMMARY

Relative tolerability and compliance must be considered in evaluation of the oral mesalamine preparations. Due to the addition of the 500 mg capsule of mesalamine controlled-release (Pentasa), daily pill burden has decreased from 16 to eight. Mesalamine controlled-release (Pentasa) is dosed four times a day using eight capsules, and mesalamine delayed-release (Delzicol) is dosed three times a day using six capsules. Another formulation of mesalamine delayed-release (Asacol HD) is available at a higher strength that also allows for three times a day dosing using six tablets. One Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Delzicol 400 mg capsules so substitution should not occur unless directed by the prescriber. Mesalamine MMX delayed-release (Lialda) is dosed once daily using two to four tablets. Mesalamine Intellicor extended-release (Apriso) is dosed once daily using four capsules. The duration of mesalamine Intellicor extended-release (Apriso) use for maintaining remission of UC beyond six months has not been evaluated.

Balsalazide (Colazal, Giazol) is indicated for UC treatment. Olsalazine (Dipentum) is indicated for UC maintenance. Balsalazide (Colazal, Giazol) differs from olsalazine (Dipentum) in that balsalazide (Colazal, Giazol) appears to have a more rapid onset of effect; it may also be slightly more effective in left-sided disease. The tolerance of olsalazine (Dipentum) 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, sRowasa enemas, Canasa suppositories) has a specific role as a non-oral treatment of distal UC, proctosigmoiditis, and proctitis. The sulfite-free mesalamine enema (sRowasa) 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.

Aminosalicylates remain first-line treatment options for mild to moderate active UC. Extended-release budesonide (Uceris) offers an alternative for induction of remission in mild to moderate UC but should not be used in maintenance of remission.

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