

Ulcerative Colitis Agents Review

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Ulcerative Colitis Agents Review

FDA-Approved Indications^{1,2,3,4,5, 6,7, 8, 9, 10}

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Oral Prodrug Forms			
balsalazide (Colaza [®])	generic	Mild to moderately active ulcerative colitis (UC)	--
olsalazine (Dipentum [®])	Alaven	--	Maintenance of remission of UC in patients intolerant of sulfasalazine
sulfasalazine (Azulfidine [®] , Azulfidine EN-tabs [®])	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.</p> <p>Treatment of rheumatoid arthritis that has not responded adequately to salicylates or other nonsteroidal anti-inflammatory agents (NSAIDs)</p> <p>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 tablets (Asacol [®])	Procter & Gamble	Mild to moderately active UC	Maintenance of remission of UC
mesalamine delayed-release tablets (Asacol [®] HD)	Procter & Gamble	Moderately active UC	--
mesalamine MMX tablets (Lialda [™])	Shire US	Mild to moderately active UC	--
mesalamine capsules (Pentasa [®])	Shire US	Mild to moderately active UC	--
mesalamine extended-release capsules (Apriso [™])	Salix	--	Maintenance of remission of UC in adults

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Topical 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	--

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.¹¹ 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.¹²

Aminosalicylates remain first line treatment options for mild to moderate active UC.¹³ 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 low systemic absorption. Several aminosalicylates are available and differ only in mode of distribution throughout the small intestine and colon.

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.¹⁴

In 2007, the American Academy of Family Physicians (AAFP) released guidelines for the diagnosis and treatment of UC. 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 topical 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®).¹⁵

The 2010 Practice guidelines of the American College of Gastroenterology state differences in treatment based on disease severity. 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 topical mesalamine is more effective than either one alone.¹⁶ 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.¹⁷ 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.¹⁸ Infliximab, a 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 the review.

Pharmacology

The first oral aminosalicylate developed, sulfasalazine, consists of a sulfapyridine carrier moiety linked to 5-ASA via an azo bond.¹⁹ Colonic bacteria cleave the azo bond, converting sulfasalazine into sulfapyridine and 5-ASA moieties.²⁰ 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.^{21,22} 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.^{23, 24}

Newer oral agents were developed to enhance 5-ASA delivery to the colon and reduce the incidence of adverse events.²⁵ The formulations fall into three categories: azo-bonded prodrug formulations (Colazal, 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.^{26,27} 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.²⁸ 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.²⁹ 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.

Mesalamine is available as suppositories (Canasa) and enemas that deliver 5-ASA directly to the site of action. For treatment of ulcerative proctitis, mesalamine suppositories (or corticosteroid foam), which deliver drug to the rectum, are appropriate for disease 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.³⁰ A new sulfite-free formulation of mesalamine enema (sfRowasa) has been FDA-approved.

Pharmacokinetics^{31,32,33,34,35,36,37,38,39,40,41,42}

All 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.

Pharmacokinetics

Drug	Delivery Mechanism	Bioavailability (%)
Oral Prodrug Forms		
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 acetatephthalate coating that retards disintegration in the stomach.	<15
Oral Delayed-Release Forms		
mesalamine 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 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 extended-release 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
Topical Forms		
mesalamine enemas (Rowasa, sfRowasa)	Topical administration	10-30
mesalamine suppositories (Canasa)	Topical administration	variable

Contraindications/Warnings^{43,44,45,46,47,48,49,50,51}

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.⁵²

Aminosalicylates are contraindicated in patients with salicylate hypersensitivity. Sulfasalazine is also contraindicated in patients with sulfonamide hypersensitivity, porphyria, and intestinal or urinary obstruction.

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.

Reports of renal impairment have 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.⁵³ A new sulfite-free mesalamine enema (sfRowasa) is now available. It is proposed to be safe for use in patients with sulfite allergy.

Drug Interactions^{54,55,56,57,58,59,60,61,62}

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.

Adverse Effects^{63,64,65, 66,67,68,69,70,71,72}

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
Oral Prodrug Forms							
balsalazide (Colazal)	6-13	5-9	2-6	8-15	4-5	nr	4-10
olsalazine (Dipentum)	10.1	5.9-17	<1	5	5	2.3	1
sulfasalazine (Azulfidine)	reported	reported	less common	more common	more common	less common	more common
Oral Delayed-Release Forms							
mesalamine tablets (Asacol)	18	7	6	35	13	6	5
mesalamine delayed-release tablets (Asacol HD)	2.3	1.7	rare	4.7	2.8	reported	1.4
mesalamine MMX tablets (Lialda)	<1	<1	reported	3.4-5.6	nr	<1	<1
mesalamine capsules (Pentasa)	1.1-1.7	3.5	0.9	2.2	1.8-3.1	1.3	1.1-1.5
mesalamine extended-release capsules (Apriso)	5	8	reported	11	4	nr	reported
Topical Forms							
mesalamine enemas (Rowasa)	8.1	2.1	3.2	6.5	5.8	2.8	<1
mesalamine enemas sulfite-free (sfRowasa)							
mesalamine suppositories (Canasa)	5.2	3.1	1.2	14.4	3.1	1.2	<1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

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.⁷³ 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 side effects of sulfasalazine are multifactorial in etiology. Some are due to the parent molecule, and some to one of its two metabolites, 5-ASA and sulfapyridine.

Reports of renal impairment 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.

Special Populations^{74,75,76,77,78,79,80,81,82}

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.⁸³ 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 is approved for use in patients five years of age and older. Other products have not been studied sufficiently in pediatric populations.

Pregnancy

Olsalazine (Dipentum) is Pregnancy Category C. All other agents in this category 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.

Dosages^{84,85,86,87,88,89,90,91,92,93,94,95}

Drug	Adults	Pediatrics	Availability
Oral Prodrug Forms			
balsalazide (Colazal)	2.25 g three times daily for eight to twelve weeks	<u>Children 5 to 17 yrs</u> 2.25 g three times daily for eight weeks OR 750 mg three times daily for eight weeks	750 mg capsule
olsalazine (Dipentum)	0.5 g twice daily	--	250 mg capsule
sulfasalazine	Treatment: 3 to 4 g daily in evenly divided doses with dosage intervals not exceeding eight hours Maintenance: 2 g daily	<u>Children 6 yrs and older</u> 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
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 MMX tablets (Lialda)	2.4 g or 4.8 g (two to four tablets) once daily with a meal for up to eight weeks	--	1.2 g delayed-release tablet
mesalamine capsules (Pentasa)	1 g four times a day for up to eight weeks	--	250 mg, 500 mg controlled-release capsules
mesalamine extended-release capsules (Apriso)	1.5 g once daily in the morning with or without food	--	0.375 mg extended-release capsules

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

Dosages (continued)

Drug	Adults	Pediatrics	Availability
Topical 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

Clinical TrialsSearch 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.

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.⁹⁶ 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.⁹⁷

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.⁹⁸ 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 controlled-release (Pentasa)

In a double-blind trial, 133 patients with UC in remission were randomized to receive balsalazide 1.5 or 3 g twice daily or mesalamine controlled-release 0.5 g three times daily.⁹⁹ Efficacy was measured by clinical activity index, endoscopy score, and histological score at 26 weeks. Balsalazide 3 g twice daily produced a significantly higher clinical remission rate (77.5 percent) than both lower dose balsalazide (43.8 percent) and mesalamine controlled-release (56.8 percent). The respective times to relapse were 161 days for high-dose balsalazide, 131 days for low-dose balsalazide ($p=0.003$ compared to high-dose balsalazide), and 144 days for mesalamine controlled-release ($p=NS$ compared to high-dose balsalazide). Pairwise contrasts of the final endoscopic score demonstrated a significant difference ($p=0.005$) between the two balsalazide treatment groups while differences among either of these two groups and mesalamine controlled-release were not statistically significant. All three treatments were well tolerated.

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.¹⁰⁰ 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.¹⁰¹ 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.¹⁰² 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.¹⁰³

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.¹⁰⁴ 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 g, respectively).

A randomized, double-blind trial compared the relapse-preventing effects of olsalazine and sulfasalazine in patients with UC over 12 months.¹⁰⁵ 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.¹⁰⁶ 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)

A twelve-month, double-blind, double-dummy, parallel-group, randomized, active comparator trial was conducted in 331 patients to evaluate the efficacy and safety of mesalamine MMX delayed-release (Lialda) 2.4 g/day compared to mesalamine delayed-release (Asacol) 1.2 g twice daily in the maintenance of left-sided UC.¹⁰⁷ All patients were in remission for at least one month prior to the trial with one or more documented relapses in the previous year. The co-primary endpoints of the study were the proportion of patients in clinical remission or clinical and endoscopic remission after 12 months of treatment. Sixty-eight percent of the mesalamine MMX group and 65.9 percent of the mesalamine delayed-release group were in clinical remission (p=0.69). Patients in clinical and endoscopic remission represented 60.9 percent of the mesalamine MMX group and 61.7 percent of the mesalamine delayed-release group (p=0.89). The diary card data did show statistical significance in treatment differences that favor the use of mesalamine MMX delayed-release. Both treatments had similar tolerability.

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.¹⁰⁸ 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.

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 (Asacol) is dosed three times a day using six tablets. 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 Asacol 400 mg tablets 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.

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.

Balsalazide (Colazal) is indicated for UC treatment. Olsalazine (Dipentum) is indicated for UC maintenance. Balsalazide (Colazal) differs from olsalazine (Dipentum) in that balsalazide (Colazal) 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, sfRowasa enemas, Canasa suppositories) has a specific role as a non-oral treatment of distal UC, proctosigmoiditis, and proctitis. 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.

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