

5-Aminosalicylic Acid Derivatives

Drug Class Review

56:36 Anti-inflammatory Agents

Balsalazide (Colazal®; Giazol®)
Mesalamine (Apriso®; Asacol HD®; Canasa®; Delzicol®; Lialda®;
Pentasa®; Rowasa; SfRowasa®)
Olsalazine (Dipentum®)
Sulfasalazine (Azulfidine®; Azulfidine EN-tabs®; Sulfazine®; Sulfazine
EC®)

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Review prepared by:
Melissa Archer, PharmD, Clinical Pharmacist
Carin Steinvoot, PharmD, Clinical Pharmacist
Bryan Larson, PharmD, BCPS, Clinical Pharmacist
Gary Oderda, PharmD, MPH, Professor

University of Utah College of Pharmacy
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Executive Summary

Introduction: Four 5-aminosalicylic acid derivatives are currently available for use in the US: balsalazide, mesalamine, olsalazine, and sulfasalazine. The 5-aminosalicylic acid derivatives are available in oral and topical formulations and are indicated in the treatment and/or maintenance of remission of ulcerative colitis.

Inflammatory bowel disease is an intestinal disorder characterized by abdominal pain, anemia, bleeding, diarrhea, and weight loss. Several inflammatory bowel disease treatments are available including: 5-aminosalicylic acid derivatives, antibiotics, corticosteroids, immunomodulators, and biological response modifiers. The 5-aminosalicylic acid derivatives are the core of drug therapy for ulcerative colitis. Current ulcerative colitis practice guidelines recommend oral 5-ASA agents for achieving and maintaining remission. Sulfasalazine is still recognized as the preferred first-line agent and balsalazide, mesalamine, and olsalazine are listed as effective alternatives.

Clinical Efficacy: The 5-aminosalicylic acid derivatives were evaluated in six meta-analyses and systematic reviews involving over 100 randomized controlled trials. According to the clinical evidence, the 5-aminosalicylic acid derivatives are more efficacious than placebo and have similar rates of efficacy when used in the treatment of ulcerative colitis. One review reported higher remission rates with sulfasalazine therapy compared to other 5-ASA agents and a second review found higher remission rates with topical-oral combination therapy compared to oral therapy alone. Two reviews reported higher rates of adverse events in sulfasalazine treatment groups compared to the other 5-aminosalicylic acid treatment groups.

Adverse Drug Reactions: The 5-aminosalicylic acid derivatives are well tolerated. The most common adverse events reported with the agents are headache and gastrointestinal upset. Adverse events are reported more frequently in patients taking sulfasalazine. Allergic reactions can occur with sulfasalazine treatment in patients with a sulfa allergy. Diarrhea adverse events are reported more frequently with olsalazine treatment. Nephrotoxicity is a rare but serious concern associated with all of the 5-aminosalicylic acid agents.

Summary: Overall, the 5-aminosalicylic acid derivatives are safe and efficacious in the treatment and prevention of ulcerative colitis. Disease therapy should be tailored to the patient and careful monitoring of efficacy and safety are important.

Introduction

Several inflammatory bowel disease treatments are currently available for use in the United States: 5-aminosalicylic acid derivatives, antibiotics, corticosteroids, immunomodulators, and biological response modifiers. Table 3 provides a summary of the inflammatory bowel disease treatments. This review will focus on the 5-aminosalicylic acid derivatives: balsalazide, mesalamine, olsalazine, and sulfasalazine. All of the agents are available in oral tablet or capsule formulations.^{1,2} Mesalamine is also available as an enema and suppository.^{1,2} The agents are broadly indicated in the treatment of ulcerative colitis. See Table 1 for a summary of the 5-aminosalicylic acid derivatives and Table 2 for a summary of the individual agent's indications.

Table 1. Comparison of the 5-Aminosalicylic Acid Derivatives^{1,2}

Agents	How supplied	Labeled Indications	Unlabeled Indications	Generic
Balsalazide (Colazal®; Giazo™)	Oral capsule: 750 mg Oral tablet: 1.1 g	Treatment of mildly- to moderately- active ulcerative colitis *Giazo™: Only approved in males ≥18 years	N/A	Yes- capsule
Mesalamine (Apriso®; Asacol HD®; Canasa®; Delzicol®; Lialda®; Pentasa®; Rowasa; SfRowasa®)	Oral capsule; delayed release: 400 mg Oral capsule; extended release: 250 mg, 500 mg Oral capsule; extended release 24hr: 0.375 g Enema: 4 g/60 mL Suppository: 1000 mg Oral tablet; delayed release: 800 mg, 1.2 g	Oral: Treatment and/or maintenance of remission of mildly- to moderately-active ulcerative colitis Rectal: Treatment of active mild-to- moderate distal ulcerative colitis, proctosigmoiditis, or proctitis	N/A	Yes- product dependent
Olsalazine (Dipentum®)	Oral capsule: 250 mg	Maintenance of remission of ulcerative colitis in patients intolerant to sulfasalazine	N/A	No
Sulfasalazine (Azulfidine®; Azulfidine EN- tabs®; Sulfazine®; Sulfazine EC®)	Oral tablet: 500 mg Oral tablet; delayed release: 500 mg	Treatment of mild-to-moderate ulcerative colitis or as adjunctive therapy in severe ulcerative colitis; enteric coated tablets are also used for rheumatoid arthritis	Ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis	Yes

Disease Overview

Inflammatory bowel disease (IBD) is an intestinal disorder characterized by abdominal pain, anemia, bleeding, diarrhea, and weight loss.^{3,4} IBD is chronic, immune-mediated and may be associated with other disorders, including ankylosing spondylitis, arthritis, cholangitis, erythema, iritis, and uveitis. The incidence of IBD varies between geographic areas and occurs with the highest incidence in Europe, the United Kingdom, and North America. Incidence of IBD has been rare in other areas but is quickly rising in Asia and Latin America. IBD is usually diagnosed in people aged 15-30 years and occurs more frequently in Jewish populations. In the United States, incidence of pediatric IBD is rapidly increasing.^{3,4} Overall, the direct medical cost for patients with UC in the US is estimated to be over \$18,000 per patient per year.⁵

Inflammatory bowel disease (IBD) can be divided into two major subtypes: Crohn's disease and ulcerative colitis.^{3,4} Crohn's disease (CD) is most commonly characterized by inflammation of the GI tract near the ileocecal valve but may occur in any part of the GI tract, often with "skip areas" containing relatively normal mucosa. The inflammation can lead to fibrosis, strictures or fistula formation. Ulcerative colitis (UC) is characterized by consistent mucosal inflammation of the colon starting at the anal verge and extending proximally, without "skip areas" as seen with Crohn's disease. CD occurs more frequently in males than females (~1.8:1) while the male to female ratio for UC is 1:1.^{3,4}

Treatment of IBD is symptomatic; currently, no curative therapies are available.³
⁴ The goal for treatment of IBD is to reduce the general inflammatory response control acute exacerbations, maintain remission, treat any related complications and improve the patient's quality of life. Unfortunately, no single agent is able to consistently accomplish this and many IBD treatment options produce limited and unpredictable effects. In addition, the disease itself exhibits fluctuations in activity and severity.^{3,4} Disease therapy should be tailored to the patient and careful monitoring of efficacy and safety are important.

Currently, treatment options for IBD are limited to antibiotics, biological response modifiers, corticosteroids, immunomodulators and 5-aminosalicylic acid derivatives.^{3,4} See Table 2 for a summary of each of these drug classes. A specific drug class may be more appropriate for one patient or for a specific disease state. For example, glucocorticoids are the treatment of choice for acute CD and UC flares but are not recommended for long-term use due to high incidence of adverse effects associated with steroid therapy. For many years, sulfasalazine was the mainstay of treatment for UC. The newer 5-aminosalicylic acid derivatives, balsalazide, mesalamine and olsalazine, were developed to provide the same therapeutic benefits of sulfasalazine but with improved tolerability. More recently, immunotherapies, such as biological response modifiers and immunosuppressants, have been used for treatment of both CD and UC.^{3,4}

The 5-aminosalicylic acid derivatives are labeled for use specifically in UC.^{1,2}
Current American College of Gastroenterology Ulcerative Colitis Practice Guidelines

(2010)⁶ recommend oral aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) for achieving and maintaining remission. According to the guidelines, topical mesalamine formulations are more effective than both topical steroids and oral aminosalicylates. The combination of oral and topical agents appears to be the most effective therapeutic option. Sulfasalazine is still recognized as the preferred first-line agent in the management of mild to moderately active colitis. Balsalazide, mesalamine, and olsalazine are listed as effective alternatives for reducing frequency of relapse.

Table 2. Labeled indications for the 5-Aminosalicylic Acid Derivatives

Agents	Treatment of mild-moderate UC	Adjunctive therapy in severe UC	Maintenance of remission of UC	Maintenance of remission in patients intolerant to sulfasalazine	Treatment of mild-moderate distal UC, proctosigmoiditis, or proctitis	Treatment of mild-moderate UC specifically in MALE patients ≥ 18 years	Treatment of mild-moderate UC in patients ≥ 5 years	Treatment of polyarticular-course juvenile RA with inadequate response to first-line options
Balsalazide	N	N	N	N	N	Y (Giazo®)	Y (Colazal®)	N
Mesalamine	Y (Asacol®; Asacol® HD; Delzicol®; Lialda®; Pentasa®)	N	Y (Asacol®; Delzicol®; Lialda®)	N	Y (Canasa®, Rowasa®, SfRowasa®)	N	N	N
Olsalazine	N	N	N	Y (Dipentum®)	N	N	N	N
Sulfasalazine	Y (Azulfidine®; Azulfidine EN®)	Y (Azulfidine®; Azulfidine EN®)	Y (Azulfidine®; Azulfidine EN®)	N	N	N	N	Y (Azulfidine EN®)

Key: UC = ulcerative colitis; RA = rheumatoid arthritis

Table 3. Summary of Inflammatory Bowel Disease Treatments^{3, 4}

Treatment Class	Agents	Route	Mechanism of Action	Monitoring	Clinical Features	Generics Available
antibiotics	metronidazole, ciprofloxacin, clarithromycin, others	Oral, IV	Used prominently in CD to manipulate the colonic flora to reduce the colonic bacteria perpetuating the inflammation of IBD	Signs and symptoms of inflammation Drug-drug Interactions Hepatic and renal function	Antibiotics can be used orally or IV Antibiotic therapy is used as adjunctive treatment of IBD, treatment for a specific complication of CD (intra-abdominal abscess and fistulas , inflammatory masses, small-bowel bacterial overgrowth and post-operative complications) and prophylaxis for recurrence in postoperative CD	Yes
biological response modifiers	adalimumab, certolizumab, infliximab, Golimumab, natalizumab	IV	Used prominently in CD to bind to and neutralize TNF-alpha which is one of the principal cytokines implicated in the T _H 1 immune response	Signs and symptoms of inflammation CBC with differential and signs of infection Acute (fever, chills, anaphylaxis) and subacute (serum sickness–like) reactions	Biological response modifiers must be injected and are infused over 2 or more hours Premedication with antihistamines, acetaminophen, corticosteroids may prevent infusion-related reactions Patients receiving biological response modifiers are at increased risk for serious infections Patients receiving biological response modifiers are at increased risk for lymphoma and other malignancies The onset of action in Crohn's disease is ~2 weeks	No
corticosteroids	budesonide, hydrocortisone, prednisone	Oral, topical, IV	Corticosteroids regulate the inflammatory process by binding to the glucocorticoid receptor which results in many specific and nonspecific effects, including anti-inflammatory, anti-proliferative and immunosuppressive	Signs and symptoms of inflammation Metabolic status (blood pressure, blood glucose, cholesterol) Electrolyte Panel With prolonged use: Bone mass density, growth in children, infection, cataracts, intraocular pressure	Corticosteroids can be used orally, topically, or IV Topical agents have fewer adverse effects but are less effective Only indicated in moderate to severe IBD Response to glucocorticoids can be characterized by responsive (remission after tapering off), dependent (relapse while tapering off), and unresponsive Long-term use of topical steroids should be limited	Yes

Treatment Class	Agents	Route	Mechanism of Action	Monitoring	Clinical Features	Generics Available
immunomodulators	azathioprine, cyclosporine, mercaptopurine, methotrexate	Oral, topical, IV	Immunosuppressive agents block actions in the immune system that are linked to the inflammatory disorder by impairing DNA and/or RNA biosynthesis, inhibiting cell proliferation or causing cell death	Signs and symptoms of inflammation CBC with differential and signs of infection Metabolic panel, including liver function tests Blood pressure Renal function	Immunosuppressants can be used to reduce or replace steroid therapies Diarrhea and ulcerative stomatitis may occur Patients receiving immunomodulators are at increased risk for lymphoma and other malignancies Patients receiving immunomodulators are at increased risk for serious infections	Yes
5-aminosalicylic acid derivatives	balsalazide, mesalamine, olsalazine, sulfasalazine	Oral, topical	Specific mechanism of action is unknown; thought to modulate inflammatory mediators (especially leukotrienes) and inhibit TNF	Signs and symptoms of inflammation Allergic reaction Renal function	First-line treatment options May be given orally or topically alone or in combination with other therapeutic agents Balsalazide, mesalamine, and olsalazine may have lower incidence of adverse events Approved for use in children ≥6 years May impair folate absorption Pregnancy Risk Factor B Photosensitivity may occur	Yes

Key: IV = intravenous; CD = Crohn's disease; IBD = inflammatory bowel disease; IOP = intraocular pressure; TNF = tumor necrosis factor

Mechanism of action

Each of the 5-aminosalicylic acid derivatives are metabolized by colonic bacteria to the active component, 5-aminosalicylic acid (5-ASA).¹⁻⁴ The exact mechanism of action of 5-ASA is not known. It appears to act topically in the gastrointestinal (GI) tract and modulate inflammatory mediators (specifically leukotrienes) and inhibit tumor necrosis factor (TNF). Table 4 provides a summary of the pharmacokinetic parameters for each of the 5-aminosalicylic acid derivatives.¹⁻⁴

Table 4. Pharmacokinetics of the 5-Aminosalicylic Acid Derivatives^{1,2}

Agents	Absorption	Distribution	Half-life	Time-to-peak	Metabolism	Renal Excretion	Active Metabolites
Balsalazide	minimal	protein binding: >99%	1.9-10.4 hrs	0.5-2 hrs	reduced in the colon	<16%	5-ASA
Mesalamine	Rectal: Variable Oral: ~20-40%	~18 L	0.5-15 hrs	Capsule: Apriso: ~4 hrs Delzicol: 4-16 hrs Pentasa: 3 hrs Rectal: 4-7 hours Tablet: Asacol: 4-12 hrs Asacol HD: 10-16 hrs Lialda: 9-12 hrs Mezavant: 8 hrs	intestinal flora and hepatic	13-30%	N-acetyl-5-aminosalicylic acid
Olsalazine	<3%	protein binding: >99%	54 min	~1 hr	colonic bacteria	<1%	5-ASA
Sulfasalazine	≤15%	~7.5 L	5.7-14.8 hrs	3-12 hrs	colonic intestinal flora and acetylation	primary route of excretion	sulfapyridine and 5-ASA

Key: 5-ASA = 5-aminosalicylic acid

Methods

A literature search was conducted to identify articles addressing clinical safety or efficacy of the 5-aminosalicylic acid derivatives, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 9/2013, evaluating efficacy of the agents are included. Trials evaluating the 5-aminosalicylic acid derivatives as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Clinical trials which evaluated pharmacokinetic studies⁷⁻¹⁶, pharmacodynamic studies^{8, 17, 18}, adverse effects studies^{19, 20}, in vivo studies²¹, adherence analyses²² and cost analyses²³⁻²⁷,
- Individual trials involving indirect comparison analyses^{19, 28-32}
- Trials involving dose-finding studies^{31, 33-37} or in indications other than the approved indications for the agent
- Individual clinical trials evaluating agents or formulations not currently available in the US^{13, 14, 38, 39} or without full access to the article^{19, 31, 36, 40-43}

Clinical Efficacy

The 5-aminosalicylic acid derivatives are evaluated in six meta-analyses and systematic reviews involving over 100 randomized controlled trials. According to the clinical evidence, the 5-aminosalicylic acid derivatives are more efficacious than placebo and have similar rates of efficacy when used in the treatment of ulcerative colitis. See the evidence tables located in the appendix for a summary of all available evidence.

Feagan et al performed two systematic reviews; one review examined the efficacy of the 5-aminosalicylic acid derivatives in patients with UC requiring treatment to achieve remission and one review examined the efficacy of the agents in maintenance of remission.^{44, 45} Forty-eight randomized controlled trials of 7776 patients with signs of symptoms of UC were examined to determine the efficacy of the 5-aminosalicylic acid derivatives in achieving remission.⁴⁵ According to the clinical data, 5-aminosalicylic acid derivatives are more efficacious than placebo in achieving of remission. No statistically significant differences in efficacy or adherence were reported between the 5-ASA agents. In addition, no significant differences were reported between once daily and multiple daily 5-ASA regimens. A subgroup analysis suggests patients with moderate disease may benefit from higher doses of 5-ASA agents. Adverse events were reported more frequently in the sulfasalazine treatment group (29%) compared to the other 5-ASA treatment groups (15%) and the most common adverse events reported in the trials included gastrointestinal upset, headache and worsening ulcerative colitis. Thirty eight randomized controlled trials of 8127 patients in remission were examined to determine the efficacy of the 5-aminosalicylic acid derivatives in maintenance of remission.⁴⁴ According to the clinical data, sulfasalazine therapy was more efficacious in maintaining remission compared to the other 5-ASA agents (relapse rate 43% vs. 48%; RR 1.14, 95%CI 1.03 to 1.27). No statistically significant differences in efficacy or adherence were found between the other 5-ASA agents or between different dosing regimens. In this trial no differences in adverse events were reported between treatment groups but most trials enrolled patients known to be tolerant to sulfasalazine which may have introduced bias in favor of sulfasalazine therapy. Common adverse events reported in this trial included headache, dyspepsia and nasopharyngitis.

Ford et al (2012)⁴⁶ performed a systematic review of 12 randomized clinical trials comparing topical 5-aminosalicylic acid derivatives to oral 5-aminosalicylic acid derivatives. In total, 761 patients with UC were included in the evaluations. No significant differences in efficacy were reported between topical and oral 5-ASA treatment groups. Improved remission rates were demonstrated with topical-oral combination therapy compared to oral therapy alone (RR of no remission = 0.65; 95 % CI = 0.47 – 0.91). No statistically significant differences in

adverse events were reported between treatment groups, although there was a trend towards lower rates of nausea and treatment discontinuation with topical therapy compared to oral therapy. Overall, it appears topical treatment in combination with oral treatment may improve efficacy without increasing adverse events.

Tong et al³⁷ and Ford et al (2011)⁴⁷ performed systematic reviews of randomized clinical trials comparing once-daily (OD) mesalamine regimens to multiple-daily (MD) mesalamine regimens. Tong et al evaluated randomized controlled trials of patients with UC. In patients with active UC, a small but statistically significant clinical benefit was observed in the OD dosing groups compared to the MD dosing groups (RR = 0.80, 95% CI 0.64–0.99). No differences in adverse event rates, treatment discontinuation rates, or adherence rates were reported between treatment groups. Ford et al (2011) evaluated randomized controlled trials of patients with UC. According to the analysis of these trials, no differences in efficacy, safety, or adherence were reported between treatment groups. Overall, it appears once daily mesalamine regimens may be as efficacious as multiple daily regimens but do not reduce the rate of adverse events or adherence.

Nikfar et al⁴⁸ conducted a meta-analysis of 20 randomized controlled trials including over 2000 patients with ulcerative colitis. Trials comparing sulfasalazine to balsalazide, mesalamine, or olsalazine were included for evaluation. According to the data, no differences in safety or efficacy were reported between sulfasalazine and each of the other 5-ASA agents. Treatment-related discontinuation rates were reported more frequently with sulfasalazine treatment compared to balsalazide treatment (RR of 0.17, CI 0.06–0.49, P = 0.001). The authors concluded that sulfasalazine should remain the treatment of choice for UC because it has a lower cost and similar rate of safety and efficacy compared to the other 5-ASA agents.

The 5-aminosalicylic acid derivatives were evaluated in six systematic reviews. In clinical trials, the 5-aminosalicylic acid derivatives were more efficacious than placebo. In general, no differences in efficacy or adherence were reported between the 5-ASA agents and regimens. One meta-analysis reported higher remission rates with sulfasalazine therapy compared to other 5-ASA agents and a second review found higher remission rates with topical-oral combination therapy compared to oral therapy alone. Adverse events were reported more frequently in the sulfasalazine treatment group compared to the other 5-ASA treatment groups in two of the systematic reviews.

Adverse Drug Reactions

The 5-aminosalicylic acid derivatives are generally well tolerated. The most common adverse events reported with the agents are headache and gastrointestinal upset.^{1, 2} Adverse effects are reported in up to 45% of patients taking sulfasalazine and are thought to be related primarily to the sulfa moiety. Adverse events reported with sulfasalazine treatment can be dose related, including headache, nausea, and fatigue, and may be minimized by taking the medicine with food or by reducing the dose. Allergic reactions can occur with sulfasalazine treatment and may include rash, including Stevens-Johnson syndrome, or other serious reactions like hepatitis, pneumonitis, and hemolytic anemia. In addition, sulfasalazine inhibits intestinal folate absorption

and patient's receiving treatment with sulfasalazine may require folate supplementation. The newer 5-aminosalicylic acid derivatives are associated with lower rates of adverse effects compared to sulfasalazine treatment. Loftus et al⁴⁹ conducted a meta-analysis of 46 randomized controlled trials involving over 6000 patients with ulcerative colitis. Overall, the frequency of adverse events reported with mesalamine treatment was comparable to placebo-treated patients and the frequency of adverse events reported with mesalamine or balsalazide treatment was lower than that of those reported with sulfasalazine treatment. Olsalazine treatment stimulates chloride and fluid secretion in the small bowel and may be associated with higher rates of diarrhea (10-20%). Nephrotoxicity is a rare but serious concern associated with 5-aminosalicylic acid treatment and renal function should be monitored in all patients receiving these agents. Table 5 provides a summary of warnings and adverse events as reported in package inserts.

Table 5. Adverse Events Reported with the 5-Aminosalicylic Acid Derivatives^{1,2}

Adverse Event	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Contraindications	None reported	Patients with hypersensitivity to sulfasalazine may react to mesalamine Note: --Apriso: Contains phenylalanine. --Canasa suppositories: Contain saturated vegetable fatty acid esters (contraindicated in patients with allergy to these components). --Rowasa enema: Contains potassium metabisulfite; may cause severe hypersensitivity reactions (ie, anaphylaxis) in patients with sulfite allergies.	None reported	Hypersensitivity to sulfa drugs Porphyria Gastrointestinal or Genitourinary obstruction
Warnings/Precautions	May cause staining of teeth or tongue if capsule is opened and sprinkled on food May cause an acute intolerance syndrome (acute abdominal pain, bloody diarrhea) Symptomatic	Use with caution in patients with hepatic and/or renal impairment Use with caution in the elderly; postmarketing reports suggest an increased incidence of blood dyscrasias in patients >65 years of age Pancreatitis,	A common adverse effect is diarrhea Use with caution in patients with hepatic and/or renal impairment Use with caution in the elderly Symptomatic worsening of UC may occur following	Fatalities associated with severe reactions including agranulocytosis, aplastic anemia, and other blood dyscrasias have occurred Deaths from irreversible neuromuscular and central nervous system changes have been reported

	worsening of UC may occur following initiation of treatment	pericarditis and myocarditis have been reported with use May cause an acute intolerance syndrome (acute abdominal pain, bloody diarrhea) Symptomatic worsening of UC may occur following initiation of treatment In males, oligospermia (rare, reversible) has been reported	initiation of treatment	Severe skin reactions (some fatal), including Stevens-Johnson syndrome (SJS), exfoliative dermatitis, and toxic epidermal necrolysis (TEN) have occurred Fatalities associated with hepatic damage have occurred In males, oligospermia (rare) and infertility has been reported Use with caution in patients with G6PD deficiency Use with extreme caution in patients with renal impairment
Adverse Events:				
Abdominal Pain	0-12%	1-18%	10%	1-10%
Anemia	4%	<3%	<1%	1-10%
Anorexia	2%	>2%	NR	>10%
Arthralgia	<5%	<6%	4%	<1%
Constipation	<2%	5%	NR	<1%
Cyanosis	NR	NR	NR	1-10%
Dermatologic reactions	NR	1-6%	1-2%	>10%
Diarrhea	0-9%	2-8%	11-17%	<1%
Dizziness	<1%	2-8%	1%	1-10%
Dysmenorrhea	3%	<1%	NR	NR
Dyspepsia	2%	1-6%	NR	>10%
Eructation	NR	16%	NR	NR
Fatigue	0-4%	<3%	NR	NR
Fever	2-6%	1-6%	<1%	1-10%
Flatulence	<3%	1-6%	<1%	NR
Flu-like syndrome	1-4%	1-5%	NR	<1%
Headache	8-15%	2-35%	NR	>10%
Hypertonia	NR	5%	NR	NR
Insomnia	2%	2%	<1%	<1%
Myalgia	<2%	3%	<1%	NR
Nausea	4-5%	3-13%	5%	>10%
Respiratory reactions	2-6%	11%	2%	<1%
Urinary tract infection	1-4%	>1%	<1%	<1%
Vomiting	0-10%	1-5%	1%	>10%

Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive; NR = not reported

Summary

Four 5-aminosalicylic acid derivatives are currently available for use in the US: balsalazide, mesalamine, olsalazine, and sulfasalazine. The 5-aminosalicylic acid derivatives are indicated in the treatment and/or maintenance of remission of ulcerative colitis. Sulfasalazine was the mainstay of treatment for UC until the newer 5-ASA derivatives were developed to provide improved tolerability. Current UC practice guidelines recommend oral 5-ASA agents for achieving and maintaining remission. Sulfasalazine is still recognized as the preferred first-line agent but balsalazide, mesalamine, and olsalazine are listed as effective alternatives. The 5-aminosalicylic acid derivatives were evaluated in six meta-analyses and systematic reviews involving over 100 randomized controlled trials. According to the clinical evidence, the 5-aminosalicylic acid derivatives are more efficacious than placebo and have similar rates of efficacy when used in the treatment of ulcerative colitis. One review reported higher remission rates with sulfasalazine therapy compared to other 5-ASA agents and a second review found higher remission rates with topical-oral combination therapy compared to oral therapy alone. The most common adverse events reported with the agents are headache and gastrointestinal upset. Adverse events are reported more frequently in patients taking sulfasalazine. Allergic reactions can occur with sulfasalazine treatment in patients with a sulfa allergy. Diarrhea adverse events are reported more frequently with olsalazine treatment. Nephrotoxicity is a rare but serious concern associated with 5-aminosalicylic acid agents. Overall, the 5-aminosalicylic acid derivatives are safe and efficacious in the treatment and prevention of ulcerative colitis.

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Evidence Tables

Reference/Study Design	N	Patient population	Treatment Interventions	Results	Adverse Effects
Feagan et al, 2012 ⁴⁵ Meta-analysis of 48 randomized controlled clinical trials	7776	Patients with UC requiring induction of remission	balsalazide mesalamine olsalazine sulfasalazine	balsalazide = mesalamine = olsalazine = sulfasalazine > placebo	sulfasalazine > balsalazide = mesalamine = olsalazine
Feagan et al, 2012 ⁴⁴ Meta-analysis of 38 randomized controlled clinical trials	8127	Patients with UC requiring maintenance of remission	balsalazide mesalamine olsalazine sulfasalazine	balsalazide = mesalamine = olsalazine = sulfasalazine > placebo	balsalazide = mesalamine = olsalazine = sulfasalazine
Ford et al, 2012 ⁴⁶ Meta-analysis of 12 randomized controlled clinical trials	761	Patients with UC	Topical mesalamine vs. Oral mesalamine or sulfasalazine	Induction: Combination therapy > monotherapy Maintenance: Intermittent topical > Oral	Topical = Oral
Tong et al, 2012 ³⁷ Meta-analysis of 10 randomized controlled trials	3410	Patients with UC requiring induction of remission of active UC and in prevention of relapse of quiescent UC	Once daily mesalamine vs. Multiple daily mesalamine	Once daily = Multiple daily	Once daily = Multiple daily
Ford et al, 2011 ⁴⁷ Meta-analysis of 8 randomized controlled trials	2741	Patients with UC requiring induction of remission of active UC and in prevention of relapse of quiescent UC	Once daily mesalamine vs. Multiple daily mesalamine	Once daily = Multiple daily	Once daily = Multiple daily
Nikfar et al, 2009 ⁴⁸ Meta-analysis of 20 randomized controlled trials	2177+	Patients with UC	balsalazide mesalamine olsalazine sulfasalazine	balsalazide, mesalamine, olsalazine = sulfasalazine > placebo	<u>Adverse event rate:</u> balsalazide, mesalamine, olsalazine = sulfasalazine <u>Withdrawal rate:</u> sulfasalazine > balsalazide