Therapeutic Class Overview
Ulcerative Colitis Agents

Therapeutic Class

- **Overview/Summary:** Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer.[3] Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology and presentation. Ulcerative colitis is limited to the rectum and colon, and affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] The 5-aminosalicylic acid (5-ASA) derivatives available in oral formulations include balsalazide, mesalamine, olsalazine and sulfasalazine. Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[4-17] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at a higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[4-16] Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[17,18]

Table 1. Current Medications Available in the Class[4-16]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Treatment of mildly to moderately active UC in patients ≥5 years of age (Colazal®), treatment of mildly to moderately active UC in male patients ≥18 years of age (Giazo®)	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)	✔
Mesalamine (Apriso®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Induction of remission in adults with active, mild to moderate UC (Lialda®), induction of remission and for the treatment of patients with mildly to moderately active UC (Pentasa®), maintenance of remission of UC in adults (Apriso®, Lialda®), treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis (Rowasa®, SfRowasa®), treatment of mildly to moderately active UC and for the maintenance of remission of UC in patients ≥5 years of age (Delzicol®), treatment of mild to moderately active ulcerative proctitis (Canasa®), treatment of moderately active UC (Asacol® HD)	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 500 mg (Pentasa®) Rectal enema: 4,000 mg/60 mL unit	✔

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		(Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)	
Olsalazine (Dipentum®)	Maintenance of remission of UC in patients who are intolerant of sulfasalazine	Capsule: 250 mg (Dipentum®)	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Prolongation of the remission period between acute attacks of UC (Azulfidine®, Azulfidine EN-tabs®), treatment of mild to moderate UC, and as adjunctive therapy in severe UC (Azulfidine®, Azulfidine EN-tabs®), Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs, (Azulfidine EN-tabs®) and treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs] (Azulfidine EN-tabs®)	Delayed-release tablet: 500 mg (Azulfidine EN-tab®, Sulfazine®†) Tablet: 500 mg (Azulfidine®, Sulfazine®†)	✔

NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis
*Generic available in at least one dosage form or strength.
†Branded generic product

Evidence-based Medicine

- A Cochrane review of the 5-aminosalicylic acid (5-ASA) derivative oral preparations for the induction of remission in patients with ulcerative colitis, demonstrates that newer 5-ASA derivatives are significantly more effective compared to placebo with no statistically significant differences between 5-ASA preparations.[19]
- Results from a meta-analysis comparing mesalamine once daily to multiple daily dosing demonstrated that once-daily dosing is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of ulcerative colitis. In addition, once-daily dosing is more effective for inducing remission in active ulcerative colitis compared to multiple daily dosing.[20]
- Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal ulcerative colitis.[21]
- In another meta-analysis, rectal 5-ASA was significantly more effective compared to placebo and rectal corticosteroids for inducing remission in ulcerative colitis. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[22]
- A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[23]
- In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy was more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active ulcerative

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colitis. Moreover, intermittent topical 5-ASA therapy was more effective compared to oral 5-ASA therapy for preventing relapse of quiescent ulcerative colitis.[24]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current guidelines by the American College of Gastroenterology, oral aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease.[25]
  - Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents more effective compared to each agent alone.[25]
  - Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is better than oral mesalamine alone. [25]
  - Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission. [25]
- Other Key Facts:
  - Balsalazide and sulfasalazine oral formulations are available generically.[18]
  - Topical mesalamine enemas are available generically.[18]

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