PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrASACOL™

5-aminosalicylic Acid Enteric Coated Tablets
Tablets, 400 mg, Oral

Mfr. Std.

Lower Gastrointestinal Anti-inflammatory

Allergan Inc.
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RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS, Renal	04/2020
WARNINGS AND PRECAUTIONS, Acute Intolerance Syndrome	03/2021
WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding	03/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Asacol (400mg of 5-aminosalicylic acid enteric coated tablets) is indicated for:

- the treatment of mild to moderate active ulcerative colitis
- the maintenance of remission of mild to moderate ulcerative colitis. Asacol at the dosage tested of 1.6 g/day may not be effective for the maintenance of remission when the underlying disease is severe.

Abrupt discontinuation may result in relapse.

1.1 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Asacol is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Asacol is contraindicated in:

- Patients with a history of sensitivity to salicylates
- Patients with severe renal impairment (GFR<30 mL/min/1.73 m^2) and/or severe hepatic impairment (see WARNINGS & PRECAUTIONS – Renal and Hepatic/Biliary/Pancreatic)
- Patients with existing gastric or duodenal ulcer
- Patients with urinary tract obstruction
- Patients unable to swallow the intact tablets

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hypersensitivity:** If toxic or hypersensitivity reactions occur, the drug should be discontinued. In assessing liver and joint complications, it should be kept in mind that these are frequently associated with ulcerative colitis.

- **Renal:** Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure has been reported in patients taking Asacol tablets as well as in patients taking other mesalamine products**.** Asacol is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy. For patients with moderate or mild renal impairment, see WARNINGS AND PRECAUTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

For the treatment of mildly to moderately active ulcerative colitis: Usual daily adult dose is 2 to 8 Asacol 400 mg tablets, taken orally in divided doses. In patients with severe active disease, the dose may be increased to 12 tablets daily.

For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 4 tablets, taken orally in divided doses. The treatment duration in a well-controlled clinical trial was 6 months.

Abrupt discontinuation is not recommended.

Ulcerative colitis rarely remits completely. Thus, it is important for patients to closely comply with the maintenance dosage prescribed by their doctors. By doing so, the risk of relapse can be substantially reduced.

Health Canada has not authorized an indication for pediatric use.

4.2 Administration

Tablets should be swallowed whole, taking care not to break the outer coating. The outer coating is designed to remain intact, to protect the active ingredient until it reaches the terminal ileum, where the tablet coating dissolves and the contents of the tablet are released into the terminal ileum and colon.

Patients should be advised to take Asacol tablets only as prescribed. The number or frequency of tablets ingested should not be changed without first consulting their physician.

Intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, the patient should be advised to consult their physician.

4.3 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double the dose.

5 OVERDOSAGE

There are no documented reports of serious human toxicity following overdose with mesalamine. Based on the adverse effect profile, symptoms that might be observed following acute overdose include headache, abdominal pain, nausea, vomiting, and diarrhea. Mesalamine is not metabolized to salicylate. There is no specific antidote and treatment is symptomatic and supportive. In treatment of acute overdose, activated charcoal and/or gastric lavage may be indicated if implemented within sixty minutes from the time of ingestion.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet, 400 mg	dibutyl phthalate, edible black ink (ammonium hydroxide, n-butyl alcohol, shellac glaze [modified] in SD-45, synthetic black iron oxide and propylene glycol), iron oxide red, iron oxide yellow, lactose, magnesium stearate, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, polyethylene glycol, polyvinylpyrrolidone, sodium starch glycolate, colloidal silicon dioxide and talc.

Asacol tablets are available for oral administration as brown-red, capsule-shaped, enteric coated tablets printed in black ink with “0752 DR”.

Each brown-red capsule-shaped enteric coated tablet of Asacol contains 400 mg mesalamine. Asacol colon-targeted tablets are coated with a special acrylic-based resin, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, which delays release of the mesalamine until the tablets reach the terminal ileum.

Asacol colon-targeted tablets are supplied in bottles of 180 tablets each.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General
Asacol and other mesalamine-containing products have differences in formulation and release characteristics that may lead to differences in concentrations of mesalamine delivered to the colon. If it is deemed necessary to switch from one mesalamine-containing product to another mesalamine-containing product, the prescriber should carefully assess the overall benefit-risk analysis based on the patient's clinical conditions and on all available information for the various mesalamine-containing products.

Acute Intolerance Syndrome
Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be re-evaluated. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. The possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on concurrent mesalamine and those with pre-existing renal disease, should be carefully monitored with urinalysis, blood urea nitrogen (BUN) and creatinine testing.

Driving and Operating Machinery
There are no data available on the effects of mesalamine on ability to drive and use machines.

Gastrointestinal
Exacerbation of the symptoms of colitis, thought to have been caused by mesalamine or sulfasalazine, has been reported in 3% of patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of Asacol tablets as well as other mesalamine products. Symptoms usually abate when Asacol tablets are discontinued.

Patients with pyloric stenosis may have prolonged gastric retention of Asacol tablets which could delay release of mesalamine in the colon.

What appears to be intact or partially intact tablets may be observed in the stool.

Hepatic/Biliary/Pancreatic
Caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with hepatic dysfunction.
In assessing liver complications, it should be kept in mind that these are frequently associated with ulcerative colitis.

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with Mesalazine products. Therefore, Asacol is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and

Asacol should only be used if the expected benefit clearly outweighs the risks to the patients. Appropriate assessment and monitoring of liver function should be performed.

Immune

Hypersensitivity

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Asacol tablets or to other compounds that contain, or are converted to, mesalamine. Asacol does not contain a sulfa moiety, thus sulfa-related side effects are avoided. Many patients with a history of sulfasalazine intolerance are able to tolerate Asacol tablets as demonstrated in open-label clinical trials. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent. In case of an allergic reaction, appropriate measures (standard of care) should be taken.

Monitoring and Laboratory Tests

It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.

It is recommended that appropriate assessment and monitoring of liver function should be performed.

Renal

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine products and pro-drugs of mesalamine. Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment. Asacol is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, history of renal disease or taking concomitant nephrotoxic drugs, caution should be exercised and Asacol should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies of Asacol use in pregnant women. Limited published data on the class of mesalamine products show an increased rate of preterm birth, stillbirth and low birth weight. These adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Mesalamine crosses the placenta. Animal reproduction studies of mesalamine found no evidence of fetal harm. Mesalamine should be used during pregnancy only if the benefits clearly outweigh the risks to the fetus.

Dibutyl phthalate (DBP) is an inactive ingredient in Asacol's enteric coating, and in animal studies at doses >95 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 should be used during pregnancy only if the potential benefit justifies the potential risk.

7.1.2 Breast-feeding

It has been reported that small amounts of 5-ASA and higher concentrations of acetyl-5-ASA are found in breast milk. While the clinical significance of this has not been determined, caution should be exercised when Asacol tablets are administered to a nursing woman.

When mesalamine is used in nursing women, infants should be monitored for changes in stool consistency. If the infant develops diarrhea, breast-feeding should be discontinued. Cases of diarrhea in breastfed infants exposed to mesalamine have been reported.

Isolated weight decrease in nursing infant has been reported during post-marketing experience with mesalamine.

Dibutyl phthalate (DBP), an inactive ingredient in the enteric coating of Asacol tablets, and its primary metabolite mono-butyl phthalate (MBP) are excreted into human milk. The clinical significance of this has not been determined.

7.1.3 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Asacol is generally well tolerated. The most commonly reported adverse reactions were nausea, diarrhea, abdominal pain and headache. Other common adverse reactions seen in clinical trials with Asacol were acute exacerbation of ulcerative colitis symptoms, abnormal hepatic functions tests and rash. Adverse events seen in clinical trials with Asacol tablets have generally been mild and reversible, and have seldom resulted in discontinuation of treatment.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two short-term (6 weeks), double-blind, placebo-controlled clinical studies involving 245 patients, 155 of whom were randomized to Asacol tablets, five (3.2%) of the Asacol patients discontinued Asacol therapy because of adverse events as compared to two (2.2%) of the placebo patients. Adverse reactions leading to withdrawal from Asacol tablets included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild

indigestion and cramping; headache, nausea, malaise, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse events occurring at a frequency of greater than 2% in these clinical trials are listed below. Overall, the incidence of adverse events seen with Asacol tablets was similar to placebo.

Headache, abdominal pain, eructation, pain, nausea, pharyngitis, dizziness, asthenia, diarrhea, back pain, fever, rash, dyspepsia, rhinitis, arthralgia, vomiting, constipation, hypertonia, flatulence, flu syndrome, chills, colitis exacerbation, chest pain, peripheral edema, myalgia, pruritus, sweating, dysmenorrhea.

Of these adverse events, only rash showed a consistently higher frequency with increasing Asacol dose in these studies.

The following adverse reactions were seen in 2% of the patients in the controlled studies: malaise, arthritis, insomnia, increased cough, acne, and conjunctivitis.

In a 6 month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to Asacol tablets, six (3.4%) of the Asacol patients discontinued Asacol therapy because of adverse events, as compared to four (4.6%) of the placebo patients. Adverse reactions leading to withdrawal from Asacol tablets included (each in one patient): anxiety; headache; pruritus, decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

In the 6 month placebo-controlled maintenance trial, the incidence of adverse events seen with Asacol tablets was similar to that seen with placebo. Adverse events occurring in Asacol 1.6 g/day group at a frequency of 2% or greater are listed in Table 1 below.

Table 1 Frequency (%) of Adverse Events Reported in the Long-Term (6 months) Double-Blind Controlled Study

Event	Asacol 0.8 g/day (n=90)	Asacol 1.6 g/day (n=87)	Placebo (n=87)
Cardiac disorders			
Chest Pain	8	8	6
Ear and labyrinth disorders			
Deaf	0	2	0
Eye disorders			
Amblyopia	1	2	0
Lacrimation Disorder	1	2	0
Vision Abnormality	1	3	0
Gastrointestinal disorders			
Abdomen Enlargement	3	2	0
Abdominal Pain	30	33	44
Colitis Flare	8	10	8
Constipation	4	13	13
Diarrhea	30	40	49
Dry Mouth	1	2	2
Dyspepsia	9	5	9
Flatulence	21	28	30

Event	Asacol 0.8 g/day (n=90)	Asacol 1.6 g/day (n=87)	Placebo (n=87)
Gastroenteritis	2	5	1
Gastrointestinal Bleeding	8	10	8
Nausea	19	17	15
Rectal Bleeding	4	2	5
Rectal Disorder	1	7	2
Stool Abnormality	7	10	8
Tenesmus	6	7	5
Vomiting	6	6	7
General disorders and administration site conditions			
Asthenia	10	20	16
Fever	12	14	13
Flu Syndrome	14	10	20
Malaise	1	5	5
Pain	19	23	11
Infections and infestations			
Infection	7	9	3
Monilia Vagina	1	2	1
Pharyngitis	22	21	15
Sinusitis	7	7	6
Musculoskeletal and connective tissue disorders			
Arthralgia	7	8	9
Arthritis	1	2	2
Back Pain	21	10	11
Hypertonia	4	5	3
Joint Disorder	2	3	0
Myalgia	7	8	5
Nervous system disorders			
Dizziness	8	8	7
Headache	52	47	49
Nervousness	6	6	2
Paresthesia	0	5	5
Somnolence	0	2	3
Psychiatric disorders			
Anxiety	3	2	2
Insomnia	4	5	5
Renal and urinary disorders			
Cystitis	0	2	0
Dysuria	1	2	1
Hematuria	0	3	1
Increased Urination	2	3	0
Reproductive system and breast disorders			
Dysmenorrhea	1	5	2
Prostate Disorder	1	2	0
Vaginitis	0	2	0
Respiratory, thoracic and mediastinal disorders			
Asthma	0	2	0
Bronchitis	3	2	2

Event	Asacol 0.8 g/day (n=90)	Asacol 1.6 g/day (n=87)	Placebo (n=87)
Epistaxis	1	2	0
Increased Cough	12	7	16
Lung Disorder	0	3	0
Rhinitis	43	40	36
Skin and subcutaneous tissue disorders			
Pruritus	2	3	7
Urticaria	0	2	1

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse reactions were seen in 1% of patients receiving Asacol 1.6 g/day in the maintenance study: migraine, ear disorder, rash, vasodilation, allergic reaction, dyspnea, chills, pneumonia, urine abnormality, peripheral edema, palpitations, anorexia, depression, urinary tract infection, leg cramps, alopecia and sweating.

In uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: Asthenia, flu syndrome, back pain, arthralgia, and rhinitis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Elevated AST or ALT, elevated alkaline phosphatase, elevated serum creatinine and BUN.

8.5 Post-Market Adverse Reactions

In addition to the adverse events listed above, the following adverse events have also been reported in controlled clinical trials, open-label studies, literature reports, or foreign and domestic marketing experience. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The relationship of the reported events to Asacol is unclear in many cases, some, including anorexia, joint pain, pyoderma gangrenosum, oral ulcers, and anemia, are sometimes part of the clinical presentation of ulcerative colitis.

Blood and lymphatic system disorders: agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy
Cardiac disorders: pericarditis (rare), myocarditis (rare)
Ear and labyrinth disorders: ear pain, tinnitus, vertigo
Eye disorders: eye pain, blurred vision
Gastrointestinal disorders: pancreatitis, gastroenteritis, gastritis, dry mouth, abdominal enlargement, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea, tenesmus
General disorders and administration site conditions: facial edema, edema, drug fever (rare), mesalamine-induced acute intolerance syndrome
Hepatobiliary disorders: hepatic impairment, including hepatic failure or hepatitis (rare), cholecystitis. Asymptomatic elevations of liver function tests have occurred in patients taking Asacol tablets. These elevations usually resolve during continued therapy or with discontinuation of Asacol. When any elevations in liver enzymes are assessed, it should be

kept in mind that hepatic complications are frequently associated with inflammatory bowel disease.
Immune system disorders: anaphylactic reaction, lupus-like syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Infections and infestations: sinusitis
Metabolism and nutrition disorders: anorexia, increased appetite
Musculoskeletal and connective tissue disorders: gout, neck pain
Nervous system disorders: somnolence, migraine, paresthesia, tremor, taste perversion, peripheral neuropathy (rare), Guillain-Barré syndrome (rare), transverse myelitis (rare)
Psychiatric disorders: anxiety, confusion, depression, emotional lability, hyperesthesia, nervousness
Respiratory, thoracic and mediastinal disorders: allergic and interstitial lung disease, eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis
Skin and subcutaneous tissue disorders: alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, Stevens-Johnson Syndrome (SJS), urticaria
Renal and urinary disorders: interstitial nephritis (rare), minimal change nephropathy (rare), nephrolithiasis, renal failure (rare) (see WARNINGS AND PRECAUTIONS), dysuria, urinary urgency, hematuria, epididymitis
Reproductive system and breast disorders: menorrhagia
Vascular disorders: vasodilation

9 DRUG INTERACTIONS

9.1 Overview

There are no known drug interactions. The effects of co-administration of Asacol tablets with cimetidine, with an antacid containing activated dimethicone and aluminum hydroxide, or with an antacid accompanied by a high fat meal were addressed in a clinical study. There were no significant *in vivo* effects on mesalamine release or the extent of drug absorption from Asacol tablets by any of the three treatments. It has been reported that simultaneous administration of famotidine, a potent H_2-antagonist, and Asacol tablets does not influence the absorption and urinary excretion of mesalamine.

9.2 Drug-Drug Interactions

Asacol tablets should not be administered with preparations which lower the stool pH, such as lactulose.

Interactions similar to acetylsalicylic acid cannot be excluded.

The hypoglycaemic effect of sulfonylureas may be enhanced when administered with aminosalicylates (oral antidiabetics may be displaced from the binding sites of plasma proteins). 5- ASA was reported to inhibit coumarin anticoagulants, resulting in thrombosis.

Concomitant treatment with mesalamine may increase the risk of myelosuppression in patients receiving azathioprine or 6-mercaptopurine. The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood dyscrasia. If concomitant use including complete blood cell counts and platelet counts.

The concurrent use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-

inflammatory drugs (NSAIDs) may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

9.3 Drug-Food Interactions

Interactions with food products have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The active ingredient in Asacol, mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), is the major active component of sulfasalazine for the treatment of inflammatory bowel disease. The available evidence suggests that mesalamine has a topical anti-inflammatory effect on the colon, where it inhibits prostaglandin and leukotriene synthesis.

10.2 Pharmacokinetics

Absorption
Human studies conducted using radiological and serum markers showed that the Asacol coating delayed release of mesalamine until the terminal ileum was reached. Other studies compared mesalamine absorption when administered as an enema (a readily available dosage form) and when released for absorption in the stomach, small intestine, and colon relative to an intravenous dose. Mesalamine release from Asacol is delayed until the terminal ileum as reflected by tmax's of about 7 hours for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid. The t1/2elm's were about 3 hours for mesalamine and 10 hours for N-acetyl-5-aminosalicylic acid. Once released in the colon, mesalamine was minimally absorbed and plasma levels were similar to those found following rectal administration. Approximately 20% of the administered dose released was absorbed, with about 80% available for topical activity in the colon. Absorption of mesalamine is similar in fasted and fed subjects.

Serum levels and urinary excretion of mesalamine and N-acetyl-5-aminosalicylic acid following single and multiple equimolar Asacol and sulfasalazine doses to healthy subjects and to patients were compared. There was no consistent trend for greater serum mesalamine or metabolite levels following Asacol dosage. Based on urinary dose recoveries, the extent of mesalamine absorption for Asacol was no greater than that for sulfasalazine. Overall, there were no meaningful differences in the extents of mesalamine absorption following equimolar Asacol and sulfasalazine doses.

In another study, there was a dose response in serum mesalamine and metabolite levels at Asacol doses of 1.2 and 2.4 g/day. In other studies when Asacol was administered at higher or lower doses than 1.2 and 2.4 g/day, serum mesalamine and N-acetyl-5-aminosalicylic acid concentrations differed from those for the 1.2 and 2.4 g/day doses as would be expected following a linear dose response relationship. The effects of co-administration of Asacol with cimetidine, an antacid containing activated simethicone and aluminum hydroxide, and antacid with a high fat meal were addressed in another study. There were no significant in vivo effects on mesalamine release or the extent of drug absorption from Asacol by any of the three treatments.

Metabolism
Mesalamine, once absorbed, is rapidly acetylated through the gut mucosal wall and by the liver.

Elimination
Mesalamine is mainly excreted by the kidney as N-acetyl-5-aminosalicylic acid.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C – 30°C).

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

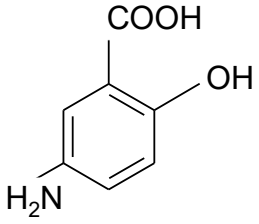
Drug Substance

Proper name: mesalamine

Chemical name: 5-amino-2-hydroxybenzoic acid, also referred to as 5-aminosalicylic acid or 5-ASA.

Molecular formula and molecular mass: $C_7H_7NO_3$ and 153.1

Structural formula:



Physicochemical properties: Mesalamine is an off-white to light-brown powder that decomposes at 280°C and is slightly soluble in water. It darkens upon exposure to air, high humidity or light over a period of several months.
pK_a Values: $pK_1 = 2.74$, $pK_2 = 5.80$.

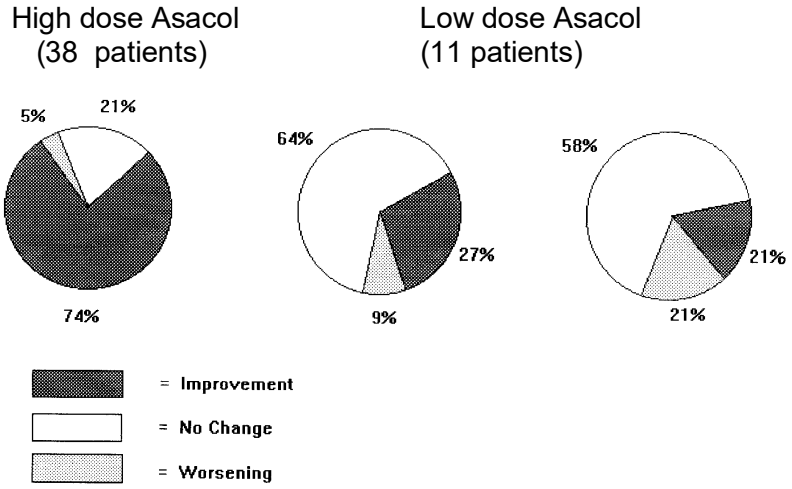
13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Mildly to moderately active ulcerative colitis:

In a randomized, double-blind, placebo-controlled clinical trial it was shown (see chart below) that Asacol (4.8 g/day of mesalamine in divided doses) was highly effective in inducing remission in ulcerative colitis patients with active disease.

OVERALL OUTCOME OF PHYSICIANS GLOBAL ASSESSMENT



13.1.1 Trial Design and Study Demographics

Maintenance of remission of ulcerative colitis:

A 6 month, randomized, double-blind, placebo-controlled, multi-centre study involved 264 patients treated with Asacol 0.8 g/day (n=90), 1.6 g/day (n=87), or placebo (n=87).

Table 2 Summary of patient demographics for clinical trials in the maintenance of remission of ulcerative colitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)
Study 1	6 month, randomized, double-blind, placebo-controlled, multi-centre study	Asacol 0.8 g/day, 1.6 g/day (n=87), or placebo (n=87)	N=264 0.8 g: n=84 1.6 g: n=87 Placebo: n =87

13.1.2 Study Results

The proportion of patients treated with 0.8 g/day who maintained endoscopic remission was not statistically significant compared to placebo. In the ITT analysis of patients treated with Asacol 1.6 g/day, Asacol maintained endoscopic remission of ulcerative colitis in 61 of 87 (70.1%) of patients, compared to 42 of 87 (48.3%) of placebo recipients (p=0.005).

A pooled efficacy analysis of 4 maintenance trials compared Asacol (0.8 to 2.8 g/day) with sulfasalazine (2 to 4 g/day). Treatment success was 58 of 98 (59%) for Asacol and 70 of 102 (69%) for sulfasalazine, a non-significant difference.

Additional double-blind clinical trials of 16, 24, and 52 weeks duration have shown Asacol in doses ranging from 0.8 to 4.4 g/day to be as effective as sulfasalazine for maintenance of remission. It is particularly noteworthy that most patients intolerant or allergic to sulfasalazine can be effectively maintained in remission on Asacol as demonstrated in open-labeled clinical trials. In addition, male infertility resulting from sulfasalazine therapy has been shown to be reversible upon treatment with Asacol.

14 NON-CLINICAL TOXICOLOGY

Acute Toxicity Studies: The acute peroral LD_{50} value for mesalamine is reported to be 5000 mg/kg in mice and 4594 mg/kg in rats.

Subacute Toxicity Studies: Rats (2/sex/group) were administered mesalamine orally at dosages of 0, 40, 120, 360, and 1080 mg/kg/day for 14 days. One female rat (1080 mg/kg/day) died, most probably of renal failure complicated by gastric mucosal injury. Drug-related changes in the clinical chemistry assays (increased serum urea nitrogen, serum creatinine and serum total proteins, and decreased albumin/globulin ratios) occurred only at the 1080 mg/kg/day level. Drug-related histomorphologic effects were present in the kidneys (1080 mg/kg/day) and gastrointestinal tracts (360 and 1080 mg/kg/day) of treated rats.

A similar study in rabbits resulted in diarrhea during the first week (males, 1080 mg/kg/day). Urinalysis revealed slight increases in proteinuria, bilirubinuria, and urinary acetone in the high dose group.

No drug-related effects were observed when rabbits were given 227.3 mg/kg/day rectally (suppository) for 12 days.

Chronic Toxicity Study: Dogs (2/sex/group) were administered Asacol tablets at oral dosages of 40, 120, and 200 mg/kg/day for one year. Control dogs received placebo tablets. Histopathology and clinical chemistry assessment showed no evidence of drug-related effects.

Teratology Studies: No evidence of teratogenicity was observed when mesalamine was administered orally at a dosage of 480 mg/kg/day to pregnant rats and rabbits.

Carcinogenicity: Dietary mesalamine was determined not to be carcinogenic in rats at doses as high as 480 mg/kg/day in one two year study, and 840 mg/kg/day in a second two year study. Similarly, dietary mesalamine was not carcinogenic in mice at 2000 mg/kg/day. These doses are 15, 26 and 62.5 times the maximum recommended human maintenance dose of Asacol of 1.6 g/day (32 mg/kg/day if 50 kg body weight assumed.)

Genotoxicity: Mesalamine was not mutagenic in two bacterial test systems (Ames assay and K. pneumoniae test) with and without metabolic activation.

Reproductive and Developmental Toxicology: The effects of oral mesalamine on fertility and gestation indices were investigated in rats at doses up to 480 mg/kg/day. No effects on fertility or gestation parameters were noted in these studies.

Special Studies: Two studies to assess the potential renal toxicity of mesalamine in a rat model have been reported in the literature. In an acute study, rats were given a single massive intravenous injection, at dose levels between 214 and 872 mg/kg. The animals killed 24-96 hours after the injection presented lesions in the proximal cortical tubules as well as renal

papillary necrosis. The former lesion was reversible by one week post-administration. In a second study, using a more clinically relevant dosing regimen, rats were dosed up to 200 mg/kg p.o. for 4 weeks. No drug-related effects were observed.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Asacol™
5-aminosalicylic acid Enteric Coated Tablets

Read this carefully before you start taking **Asacol** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Asacol**.

Serious Warnings and Precautions

- **Stop taking Asacol if you have an allergic reaction to this drug. Speak to your doctor immediately or go to the nearest emergency department. Symptoms of allergic reaction may include itching, hives, swelling in face or hands, tightness in chest, trouble breathing.**
- **Asacol contains the medicinal ingredient mesalamine. Kidney failure has been reported in patients taking Asacol as well with drugs that contain mesalamine.**
- **Speak to your doctor if you have a history of kidney problems before using Asacol. Taking Asacol may worsen your kidney condition. Your doctor may check your kidney function before you begin Asacol and during your treatment.**

What is Asacol used for?

- To treat symptoms related to ulcerative colitis when the condition of the disease is mild to moderate. Ulcerative colitis is where the large bowel (colon) and back passage (rectum) becomes red and swollen (inflamed).
- To help prevent a moderate to mild condition of ulcerative colitis from returning.

How does Asacol work?
Asacol is an anti-inflammatory drug for the bowel. Asacol is believed to stop the production of certain substances in your body that cause swelling (inflammation). Asacol tablets are designed to prevent the medicine from being released early.

What are the ingredients in Asacol?
Medicinal ingredients: mesalamine, otherwise known as 5-aminosalicylic acid (5-ASA)
Non-medicinal ingredients: colloidal silicon dioxide, dibutyl phthalate, edible black ink (ammonium hydroxide, n-butyl alcohol, shellac glaze [modified] in SD-45, synthetic black iron oxide and propylene glycol), Eudragit®-S {methacrylic acid copolymer Type B (USP)}, iron oxide red, iron oxide yellow, lactose, magnesium stearate, polyethylene glycol, polyvinylpyrrolidone, sodium starch glycolate and talc.

Asacol comes in the following dosage form:
400 mg tablets

Do not use Asacol if:

- You are allergic to mesalamine (5-ASA) or any of the ingredients in Asacol.
- You have a history of sensitivity to salicylates, for example acetylsalicylic acid (i.e. Aspirin®).
- You have severe liver problems.
- You have severe kidney problems.
- You have an ulcer in the stomach or intestines.
- You have a blocked urinary tract.
- You are unable to swallow the whole tablet.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Asacol. Talk about any health conditions or problems you may have, including if you:

- have higher than normal blood urea nitrogen (BUN) levels (renal function test)
- have a history of kidney problems
- are taking other ulcerative colitis drugs that contain Mesalamine. Speak to your doctor before switching your treatment to Asacol.
- had an allergic reaction to sulfasalazine. Stop taking Asacol and speak to your doctor if you experience a rash or a fever.
- have pyloric stenosis. Pyloric Stenosis is a condition in where the passage from the stomach to the small intestine is narrow or blocked. Pyloric stenosis may keep the Asacol tablet from reaching the colon as quickly as it normally would.

Other warnings you should know about:

Treatment with Asacol can increase your risk of certain side effects, including:

- **Liver problems**: You may develop liver function problems, including liver failure.
- **Kidney Stones**: You may develop kidney stones when using Asacol. Be sure to drink enough liquids while you are taking Asacol. Speak to your doctor about how much water or other liquids you should be drinking. Symptoms of kidney stones may include:
    - blood in urine
    - urinating more often
    - pain in back, side, stomach and groin
- **Acute Intolerance Syndrome:** Mesalamine, the medicinal ingredient in Asacol, can cause acute intolerance syndrome. Your doctor may monitor your kidney function if you have kidney disease while on treatment. Speak to your doctor immediately if you experience any of the following symptoms:
    - cramping
    - sudden abdominal pain
    - bloody diarrhea
    - fever
    - headache
    - rash
- **Colitis (inflamed colon):** Asacol can cause the symptoms of colitis to worsen. Speak to your doctor immediately if you suddenly experience any of the following symptoms:
    - abdominal pain
    - bloody diarrhea
    - fever
    - headache
    - rash or itchy skin

- eye infection

Pregnancy and breastfeeding:
If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.

- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with Asacol.
- Taking mesalamine during pregnancy have been reported to cause:
  - early Labor
  - stillbirth (death of baby)
  - low birth weight of baby
- If you breastfeed your baby while taking Asacol, your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea. Your doctor may advise you to stop breastfeeding your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Asacol:

- aminosalicylates. Taking Asacol with aminosalicylates may increase your risk of developing a blood clot.
- azathioprine, 6-mercaptopurine. Taking Asacol with these drugs may increase your risk of developing a blood disorder.
- medicines that can change the acidity level of the stool, such as lactulose
- medicines to treat ulcers such as cimetidine, famotidine
- nonsteroidal anti-inflammatory drugs (NSAID). Taking Asacol with these drugs may increase your risk of side effects to your kidneys.

Treatment with Asacol can affect the results of a urine test. Tell your doctor or nurse that you are taking Asacol when taking a urine test.

How to take Asacol:

- Take Asacol exactly as your doctor tells you to take it. Do NOT take more of it than prescribed. Speak to your doctor or pharmacist if you are not sure.
- Take the exact dose your doctor tells you to take during remission. Following your doctor's instructions can reduce the risk of your symptoms returning.
- Do NOT stop using Asacol abruptly.
- Swallow tablets whole. Do NOT crush or chew the tablet.
- The whole tablet or a part of it may occasionally appear in your stool. Speak to your doctor if this occurs frequently.

Usual Adult Dose:
Treatment of moderate to mild ulcerative colitis:

- Take two to eight 400 mg tablets daily in divided doses.
- Your doctor may increase your daily dose to twelve 400 mg tablets if your condition is severe.

Treatment for the maintenance of remission of ulcerative colitis**:**
Take four 400 mg tablets daily in divided doses.

Overdose:

If you think you have taken too much Asacol, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible.
However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double the dose.

What are possible side effects from using Asacol?

These are not all the possible side effects you may feel when taking Asacol. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- acne
- aches and muscle cramps
- constipation
- coughing
- chills
- diarrhea
- dizziness
- dry mouth
- feelings of confusion, anxiety or nervousness
- hair loss
- headache or migraine
- increased appetite
- joint and groin pain
- lower back discomfort or back pain
- low energy or feeling unwell
- menstrual (period) pain
- nausea and vomiting
- rash
- runny nose
- sore throat
- stuffy head
- sweating

Your doctor may run tests, including a blood test, to check your liver function and blood cell counts.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Worsening of your ulcerative colitis symptoms		✓	
UNCOMMON			
Kidney stones (hard little pebbles that form in your kidneys) blood in urine, urinating more often, pain in your back, side, belly or groin		✓	
Eye problems: itchy, red eyes with discharge, pain, swelling and blurred vision		✓	
Ear problems: ear pain	✓		
Pneumonia (infection in the lungs): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath			✓
Fast heartbeat: pounding, fluttering, racing, skipping beats, chest discomfort or shortness of breath			✓
Chest pain		✓	
Stomach pain		✓	
RARE			
Fever (higher than normal body temperature)		✓	
Allergic (hypersensitivity) reactions itching; rash, swelling of face or hands, tightness in chest, trouble breathing			✓
Lung problems (thickening and scaring of lung tissues): Shortness of breath, fast, shallow breathing, dry cough		✓	
Kidney problems changes in urine output, cloudy or tea-coloured urine, blood in the urine, weight gain (from retaining fluid), confusion, swelling of the eyes, hands, legs, and feet Additional less specific symptoms may include: drowsiness, fatigue, nausea, vomiting, rash, persistent itching, and back pain		✓	
Liver problems severe abdominal pain or distension, nausea, vomiting, drop in appetite, bloating, together with yellowing of the skin and eyes, and abnormal liver function tests		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Acute intolerance syndrome cramping, stomach pain, bloody and excessive stools, fever, headache and rash			✓
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Asacol should be stored at controlled room temperature (15℃ – 30℃).

Keep out of reach and sight of children.

If you want more information about Asacol:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.allergan.ca, or by calling 1-800-668-6424.

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