

PRODUCT MONOGRAPH

PrASACOL[®]

5-aminosalicylic Acid Enteric Coated Tablets, 400 mg, Mfr. Std.

Lower Gastrointestinal Anti-inflammatory

Allergan Inc.
85 Enterprise Blvd., Suite 500
Markham, Ontario
L6G 0B5
www.allergan.ca

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PRODUCT MONOGRAPH

PrAsacol®

5-aminosalicylic Acid Enteric Coated Tablets, 400 mg, Mfr. Std.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Enteric coated tablet 400 mg	Lactose <i>For a complete listing see Dosage Forms, Composition and Packaging Section</i>

INDICATIONS AND CLINICAL USE

Asacol 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.

Pediatrics:

Safety and effectiveness of Asacol therapy in children have not been established.

CONTRAINDICATIONS

Asacol is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of this product monograph
- Patients with a history of sensitivity to salicylates
- Patients with severe renal impairment ($GFR < 30 \text{ ml/min/1.73m}^2$) 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
- Infants under 2 years of age

WARNINGS AND PRECAUTIONS

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.

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.

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

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.

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, 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.

Special Populations

Pregnancy: 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.

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.

Nursing Women: 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.

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.

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.

ADVERSE REACTIONS

Adverse Drug 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

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates of occurrence.

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	Placebo (n=87)	Asacol 0.8 g/day (n=90)	Asacol 1.6 g/day (n=87)
Headache	49	52	47
Rhinitis	36	43	40
Diarrhea	49	30	40
Abdominal Pain	44	30	33
Flatulence	30	21	28
Pain	11	19	23
Pharyngitis	15	22	21
Asthenia	16	10	20
Nausea	15	19	17
Fever	13	12	14
Constipation	13	4	13
Back Pain	11	21	10
Flu Syndrome	20	14	10
Colitis Flare	8	8	10
Gastrointestinal Bleeding	8	8	10
Stool Abnormality	8	7	10
Infection	3	7	9
Dizziness	7	8	8
Chest Pain	6	8	8
Arthralgia	9	7	8
Myalgia	5	7	8
Increased Cough	16	12	7
Sinusitis	6	7	7
Tenesmus	5	6	7
Rectal Disorder	2	1	7
Vomiting	7	6	6
Nervousness	2	6	6
Dyspepsia	9	9	5

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

Event	Placebo (n=87)	Asacol 0.8 g/day (n=90)	Asacol 1.6 g/day (n=87)
Insomnia	5	4	5
Hypertonia	3	4	5
Gastroenteritis	1	2	5
Malaise	3	1	5
Dysmenorrhea	2	1	5
Paresthesia	5	0	5
Pruritus	7	2	3
Joint Disorder	0	2	3
Increased Urination	0	2	3
Vision Abnormality	0	1	3
Hematuria	1	0	3
Lung Disorder	0	0	3
Rectal Bleeding	5	4	2
Anxiety	2	3	2
Bronchitis	2	3	2
Abdomen Enlargement	0	3	2
Arthritis	2	1	2
Dysuria	1	1	2
Monilia Vagina	1	1	2
Amblyopia	0	1	2
Dry Mouth	0	1	2
Epistaxis	0	1	2
Lacrimation Disorder	0	1	2
Prostate Disorder	0	1	2
Somnolence	3	0	2
Urticaria	1	0	2
Asthma	0	0	2
Cystitis	0	0	2
Deaf	0	0	2
Vaginitis	0	0	2

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.

Abnormal Hematologic and Clinical Chemistry Findings: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated serum creatinine and BUN.

Post-Market Adverse Drug 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.

Body as a Whole: Neck pain, abdominal enlargement, facial edema, edema, lupus-like syndrome, drug fever (rare).

Cardiovascular: Pericarditis (rare), myocarditis (rare), vasodilation, migraine.

Digestive: Anorexia, pancreatitis, gastroenteritis, gastritis, increased appetite, dry mouth, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea, tenesmus.

Hematologic: Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Immunological: Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS)

Musculoskeletal: Gout.

Nervous: Anxiety, depression, somnolence, emotional lability, hyperesthesia, vertigo, nervousness, confusion, paresthesia, tremor, peripheral neuropathy (rare), Guillain-Barré syndrome (rare), and transverse myelitis (rare).

Respiratory/Pulmonary: Sinusitis, eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

Skin: Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria.

Special Senses: Ear pain, eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Interstitial nephritis (rare), minimal change nephropathy (rare), nephrolithiasis, renal failure (rare) (see WARNINGS AND PRECAUTIONS), dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.

Hepatic: 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.

DRUG INTERACTIONS

Drug-Drug Interactions

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 H₂-antagonist, and Asacol tablets does not influence the absorption and urinary excretion of mesalamine.

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

Interactions similar to acetylsalicylic acid cannot be excluded.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with ulcerative colitis should be made aware that 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.

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.

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.

Administration

1. 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.
2. 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.
3. Intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, the patient should be advised to consult their physician.

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.

ACTION AND CLINICAL PHARMACOLOGY

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.

Asacol tablets have a special acrylic-based resin coating, which does not allow the drug to be released below pH 7. The coating delays release of mesalamine until the tablets reach the terminal ileum and colon. Once released in the colon, mesalamine is minimally absorbed and plasma levels are similar to those found following rectal administration of mesalamine.

Approximately 20% of the administered dose released in the colon is absorbed, the remainder is available for colon therapeutic activity and excretion in the feces. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated through the gut mucosal wall and by the liver. It is mainly excreted by the kidney, as N-acetyl-5-aminosalicylic acid.

STABILITY AND STORAGE RECOMMENDATIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.

Each tablet contains the following inactive ingredients: 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 colon-targeted tablets are supplied in bottles of 180 tablets each.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

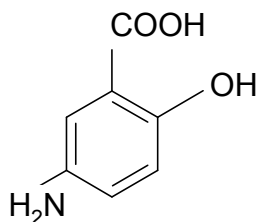
Drug Substance

INN: mesalazine

USAN: mesalamine

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

Structural Formula:



Molecular Formula: $C_7H_7NO_3$

Molecular Weight: 153.1

Description: 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.

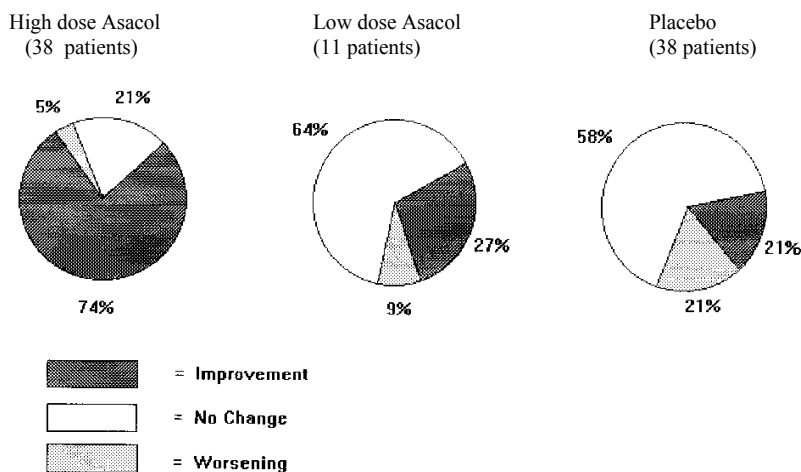
pK_a Values: pK₁ = 2.74, pK₂ = 5.80.

CLINICAL TRIALS

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



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). 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.

DETAILED PHARMACOLOGY

Pharmacokinetics: Mesalamine release from Asacol is delayed until the terminal ileum as reflected by t_{max} 's of about 7 hours for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid. The $t_{1/2_{elm}}$'s were about 3 hours for mesalamine and 10 hours for N-acetyl-5-aminosalicylic acid.

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. 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. The absorbed mesalamine was rapidly acetylated through the gut mucosal wall and by the liver. It was mainly excreted by the kidney as N-acetyl-5-aminosalicylic acid.

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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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.)

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

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.

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PART III CONSUMER INFORMATION

**PrAsacol®
5-aminosalicylic acid Enteric Coated Tablets,
400 mg, Mfr. Std.**

This leaflet is part III of a three-part "Product Monograph" published when Asacol was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Asacol. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Asacol is used for the treatment of mild to moderate ulcerative colitis and the maintenance of remission of mild to moderate ulcerative colitis.

What it does:

Ulcerative colitis involves chronic inflammation of the inner lining of the colon and rectum. Asacol reduces inflammation right at the site.

When it should not be used:

Asacol is not suitable for everyone. It should not be used if:

- You are allergic to this drug or to any ingredient in the formulation or component of the container (see below for ingredient listing)
- 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 stomach or intestinal ulcer
- You have urinary tract obstruction
- You are unable to swallow the intact tablet
- The patient in question is an infant under 2 years of age

What the medicinal ingredient is:

5-aminosalicylic acid (5-ASA)

What the important nonmedicinal ingredients are:

Each tablet contains the following inactive ingredients: 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.

What dosage forms it comes in:

Asacol 400 mg tablets are available for oral administration as brown-red, capsule-shaped, enteric-coated tablet, printed in black ink with "0752 DR".

Asacol (400 mg tablets) is supplied in bottles of 180 tablets each.

WARNINGS AND PRECAUTIONS

Some patients who have experienced an allergic reaction to sulfasalazine may have a similar reaction to Asacol or to other products that contain, or are converted to, 5-ASA. Asacol does not contain sulfa.

The development of some cases of liver function problems, including liver failure, have been reported in patients who were using medication similar to or the same as that contained in Asacol.

Serious Warnings and Precautions

If you have an allergic reaction to Asacol, stop taking the medication and either consult your doctor 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.

Kidney failure has been reported in patients taking products with mesalamine, the active ingredient in Asacol. If you have a history of kidney problems, you should tell your doctor before using Asacol, as it may worsen your kidney condition. Your doctor may require certain tests to check your kidney function before starting Asacol therapy and periodically while you continue Asacol therapy.

Talk with your doctor about your medical history and if you have any questions about your medication. It's also important to visit your doctor periodically to monitor your condition and discuss how your treatment plan is working for you

BEFORE you use Asacol talk to your doctor or pharmacist if:

- You have any liver or kidney problems
- You are pregnant, become pregnant, or are a nursing mother. Small amounts of 5-aminosalicylic acid and its metabolite have been found in human breast milk. Dibutyl phthalate (DBP), an inactive ingredient in the enteric coating of Asacol tablets, and its primary metabolite monobutyl phthalate (MBP) are also excreted into human milk. Caution should be taken when using Asacol while you are nursing. Discuss with your doctor.
- You have pyloric stenosis (a narrowing of the outlet from the stomach that causes contents of the stomach to remain there for a longer period of time). Pyloric stenosis may keep the Asacol tablet from reaching the colon as quickly as it normally would.

Kidney stones may develop with use of mesalazine. Symptoms may include blood in urine, urinating more often, pain in your back, side, belly or groin. Be sure to drink enough liquids while you are taking Asacol. Talk to your doctor about how much water or other liquids you should be drinking.

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of Asacol or the effects of other medicines may be changed. Please check with your doctor or pharmacist before taking other medications with Asacol.

Asacol tablets should not be taken with drugs that can change the acidity level of the stool, such as lactulose.

Asacol can be taken with or without food.

PROPER USE OF THIS MEDICATION

Ulcerative colitis rarely disappears completely. Therefore it is important to closely follow your doctor’s dosage instructions. This can reduce the risk of symptoms re-appearing.

Do not stop taking the medication abruptly.

Usual dose:

Treatment: The usual daily adult dose is 2 to 8 Asacol tablets, taken orally, in divided doses. In severe disease the dose may be increased to 12 Asacol tablets daily.

Maintenance of remission: The recommended daily dosage in adults is 4 Asacol tablets, taken orally, in divided doses.

When taking Asacol, you should:

1. Swallow tablets whole. Take care not to break or chew the tablet, as this breaks the special outer coating.
2. Take Asacol tablets only as prescribed. Do not change the number or frequency of tablets ingested without first consulting your doctor.
3. What appears to be intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, consult your doctor.

If you have questions about your medication, please contact your doctor or pharmacist.

Overdose:

In case of drug overdose, contact a health care practitioner, 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Asacol is generally well tolerated, however, side effects may occur with its use.

The most commonly reported side effects included nausea, diarrhea, abdominal pain and headache. Other common adverse reactions seen with Asacol were worsening of ulcerative colitis symptoms, abnormal liver function tests and rash.

Inform your doctor, if you experience worsening of your ulcerative colitis symptoms, fever, rash, chest pain or stomach pain, or difficulty breathing while taking Asacol.

IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common (more than 1 in 100)			
Worsening of your ulcerative colitis symptoms		✓	
Uncommon			
Kidney stones (hard little pebbles that form in your kidneys) – symptoms include blood in urine, urinating more often, pain in your back, side, belly or groin.		✓	
Rare (less than 1 in 1,000)			
Fever		✓	
Allergic reactions which may include symptoms such as: itching; rash, swelling of face or hands, tightness in chest, trouble breathing			✓
Kidney problems which may include symptoms such as: 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		✓	

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IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor
		✓	
Liver problems which may include symptoms such as: severe abdominal pain or distension, nausea, vomiting, drop in appetite, and bloating, together with yellowing of the skin and eyes.		✓	

This document plus the full product monograph, prepared for health professionals is available by contacting the sponsor, Allergan Inc. at 1-800-668-6424.

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This is not a complete list of side effects. For any unexpected effects while taking Asacol, contact your doctor or pharmacist.

HOW TO STORE IT

Asacol should be stored at controlled room temperature (15°C - 30°C).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

More information can be found on the Internet at: <http://www.allergan.ca>