PRODUCT MONOGRAPH

Pr ASACOL® 800

Mesalamine Delayed-Release Tablets*, Mfr. Std.

Lower Gastrointestinal Anti-inflammatory

Warner Chilcott Canada Co.
Mississauga, Ontario, L5N 6J5

Date of Revision:
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Asacol is a registered trademark of Medeva Pharma Suisse AG
Liestal, Switzerland

Control No.: 178871

* also referred to as 5-aminosalicylic acid (5-ASA)

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Mesalamine Delayed-Release Tablets, Mfr. Std.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Mesalamine Delayed Release Tablets, 800 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging Section.*

INDICATIONS AND CLINICAL USE

ASACOL 800 (800 mg tablet; mesalamine or 5-aminosalicylic acid) is indicated for:
- treatment of moderately active ulcerative colitis.

In the pivotal clinical trial with Asacol 800 (800 mg tablet), moderately active ulcerative colitis was determined by a Physician Global Assessment (PGA) which included clinical and endoscopic evaluations scored as a 2 on a 0 (normal) to 3 (severe) scale.

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely. Abrupt discontinuation of mesalamine therapy is not recommended, and may result in relapse. It is important for patients to comply with the dosage prescribed by their doctors; by doing so, the risk of relapse can be substantially reduced.

Relevant clinical information:
Findings from the clinical studies for Asacol 800 (800 mg tablet), that a higher dose of mesalamine shows greater efficacy in patients with moderately active disease, is consistent with previous findings seen with Asacol (400 mg tablet). The demonstrated efficacy of Asacol 800 (800 mg tablet) administered at 4.8 g/day in patients with moderately active disease offers this patient population convenient dosing over Asacol (400 mg tablet) tablets by reducing the number of tablets by half. For information on the Clinical Efficacy and Safety of Asacol 800 (800 mg tablet) obtained from the Clinical Trials, please refer to the section "CLINICAL TRIALS" below. **Interchangeability between Asacol (400 mg tablet) and Asacol 800 (800 mg tablet)**

has not been established. For information on the Asacol (400 mg tablet), please refer to the current Product Monograph for the Asacol (400 mg tablet) tablet.

Geriatrics:
No data are available.

Pediatrics:
Clinical trials of Asacol 800 (800 mg tablet) did not include pediatric patients. Asacol 800 (800 mg tablet) is contraindicated in patients unable to swallow an intact tablet and in patients less than 2 years of age.

CONTRAINDICATIONS

ASACOL 800 (800 mg tablet) 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 the DOSAGE FORMS, COMPOSITION AND PACKAGING section of this product monograph.
- patients with a history of sensitivity to salicylates
- Patients with severe renal impairment (GFR<30ml/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 tablet and
- 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 and acute and chronic interstitial nephritis, and renal failure has been reported in patients taking mesalamine products. Asacol 800 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 800 (800 mg tablet) tablets and periodically while on Asacol 800 (800 mg tablet) therapy. For patients with moderate or mild renal impairment, see WARNING AND PRECAUTIONS.

General
Asacol 800 (800 mg tablet) 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.

Carcinogenesis and Mutagenesis
Preclinical animal data are provided in the Toxicology section.

Gastrointestinal
Acute exacerbation of the symptoms of colitis, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported in 3% of patients in controlled clinical trials of Asacol (400 mg tablet) versus sulfasalazine. This reaction has been reported after initiation of other mesalamine-containing products, and was reported by 2% of patients receiving Asacol 800 (800 mg tablet) in two controlled clinical trials. Symptoms usually abate when mesalamine therapy is discontinued.

Patients with pyloric stenosis may have prolonged gastric retention of Asacol 800 (800 mg tablet) tablets that 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 800 (800 mg tablet) (or other compounds that 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 800 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 800 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 800 (800 mg tablet) tablets or to other compounds that contain, or are converted to, mesalamine. Asacol 800 (800 mg tablet) does not contain a sulfa moiety, thus sulfa-related side effects are avoided.

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. Asacol 800 is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, caution should be exercised and Asacol 800 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

Pregnant Women: There are no adequate and well controlled studies of Asacol 800 (800 mg tablet) 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 800 (800 mg tablet)'s enteric coating, and in animal studies at doses >80 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:

Literature reports indicate that, following oral or rectal administration of mesalamine-containing products to lactating women, small amounts of 5-ASA and higher concentrations of the metabolite N-acetyl-5-ASA are found in breast milk. While the clinical significance of this has not been determined, caution should be exercised when Asacol 800 (800 mg tablet) tablets are administered to a nursing woman.

Dibutyl phthalate (DBP), an inactive ingredient in the enteric coating of Asacol 800 (800 mg tablet), and its primary metabolite mono-butyl phthalate (MBP) are excreted into human milk. The clinical significance of this has not been determined.

Pediatrics:

Safety and effectiveness of Asacol 800 (800 mg tablet) therapy in patients younger than 18 years of age has not been established.

Geriatrics:

Less than 10% of patients in the Asacol 800 (800 mg tablet) clinical trial were $\geq$ 65 years of age. Patients in this age range were not significantly different from the overall patient population with respect to safety and efficacy responses.

Monitoring and Laboratory Tests

It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol 800 (800 mg tablet) tablets and periodically while on Asacol 800 (800 mg tablet) 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 approximate rates of occurrence.

In two double-blind, randomized 6 week, parallel-group design clinical trials in patients with mildly to moderately active ulcerative colitis, the safety and efficacy of Asacol 800 (800 mg tablet), dosed at 4.8 g/day, was compared to the safety and efficacy of Asacol (400 mg tablet), dosed at 2.4 g/day. In these trials, the overall incidence of adverse events was comparable between the two treatment groups, and similar to that observed previously with Asacol (400 mg tablet) therapy. Table 1 presents adverse events assessed as possibly or probably related to the study drug in 1% or more of patients in either treatment group.

Table 1
Adverse Events Assessed as Possibly or Probably Related to Study Drug
Occurring in >=1% in Either Treatment Group
by MedDRA PT

MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=349) n (%)	4.8g/day Asacol (800 mg Tablet) (N=338) n (%)
Headache	13 (3.7%)	12 (3.6%)
Nausea	6 (1.7%)	8 (2.4%)
Vomiting	3 (0.9%)	4 (1.2%)
Abdominal pain	7 (2.0%)	3 (0.9%)
Ulcerative colitis	4 (1.1%)	3 (0.9%)
Abdominal distension	5 (1.4%)	1 (0.3%)

Post-Market Adverse Drug Reactions

In addition to the adverse events reported above in the two clinical trials involving Asacol 800 (800 mg tablet), the following adverse events have been reported in controlled clinical trials, open-label studies, literature reports, or foreign and domestic marketing experience with Asacol (400 mg tablet) or other products that contain or are metabolized to mesalamine. 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, and some may be part of the clinical presentation of ulcerative colitis.

Body as a Whole: Allergic reaction, facial edema, edema, peripheral edema, asthenia, drug fever (rare), chills, malaise, pain, neck pain, chest pain, back pain, abdominal enlargement, lupus-like syndrome, flu syndrome, infection.

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

Digestive: Dry mouth, stomatitis, oral ulcers, anorexia, increased appetite, dyspepsia, eructation, flatulence, pancreatitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer (rare), constipation, rectal hemorrhage, bloody diarrhea, tenesmus, rectal disorder, stool abnormality.

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.

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

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

Musculoskeletal: Gout, rheumatoid arthritis, arthritis, arthralgia, joint disorder, myalgia, hypertonia, leg cramps.

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

Respiratory/Pulmonary: Epistaxis, rhinitis, sinusitis, pharyngitis, dyspnea, increased cough, asthma exacerbation, pleuritis, bronchitis, pneumonia, eosinophilic pneumonia, interstitial pneumonitis, lung disorder.

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

Special Senses: Ear pain, tinnitus, deafness, ear congestion, ear disorder, conjunctivitis, eye pain, amblyopia, blurred vision, vision abnormality, lacrimation disorder, taste perversion.

Urogenital: Interstitial nephritis (rare), minimal change nephropathy (rare), renal failure (rare) (See also WARNINGS AND PRECAUTIONS), cystitis, urinary tract infection, dysuria, urinary urgency, increased urination, hematuria, urine abnormality, epididymitis, prostate disorder, decreased libido, dysmenorrhea, menorrhagia, vaginitis, vaginal moniliasis.

Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated serum creatinine and BUN.

DRUG INTERACTIONS

Overview

There are no known drug interactions with Asacol (400 mg tablet). No drug interaction studies were performed with Asacol 800 (800 mg tablet). In clinical trials of Asacol 800 (800 mg tablet), there were no restrictions on the concomitant use of antacids, H_2-receptor antagonists, proton-pump inhibitors, or other preparations affecting gastrointestinal pH. In subgroup analyses, patients receiving H_2-receptor antagonists or proton-pump inhibitors were not significantly different from the overall patient population with respect to safety and efficacy response.

Drug-Food Interactions

Administration of the Asacol 800 (800 mg tablet) tablet immediately following a high fat meal had no significant effect on the extent of exposure to 5-ASA and N-acetyl-5-ASA based on AUC and percent of dose excreted in urine (Ae%). A reduction of approximately 50% was observed in C_{max}, due to significantly delayed t_{max} when dosed following a high fat meal compared to dosing under fasting condition. However, no impact was observed on the safety profile or systemic exposure to 5-ASA and N-acetyl-5ASA in the clinical trials where doses were given without regards to meals. Therefore, Asacol 800 (800 mg tablet) can be taken in a fasted or fed state.

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.[23,24,25]

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely. Abrupt discontinuation of Asacol 800 (800 mg tablet) is not recommended, and may result in relapse. It is important for patients to comply with the 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 moderately active ulcerative colitis: Usual daily adult dose is 6 Asacol 800 (800 mg tablet) tablets, taken orally in divided doses. Asacol 800 (800 mg tablet) may be given without regards to meals.

For alternate dosing for moderately active ulcerative colitis, see the Asacol (400 mg tablet) Product Monograph.

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. Swallow tablets 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. Take Asacol 800 (800 mg tablet) tablets only as prescribed. Do not change the number or frequency of tablets ingested without first consulting your physician.
3. What appears to be intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, consult your physician.

OVERDOSAGE

There is no clinical experience with overdose of Asacol 800 (800 mg tablet). Mesalamine is not metabolized to salicylate. There is no specific antidote for mesalamine overdose, and treatment is symptomatic and supportive.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient in Asacol 800 (800 mg tablet) is mesalamine (5-aminosalicylic acid, also referred to as 5-ASA). The available evidence suggests that mesalamine has a topical anti-inflammatory effect on the colon, where it inhibits prostaglandin and leukotriene synthesis.

Pharmacodynamics

Asacol 800 (800 mg tablet) 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. Asacol 800 (800 mg tablet) demonstrated expected enteric coating properties that were comparable to those of the Asacol (400 mg tablet) tablet, as indicated by *in-vitro* dissolution data as well as prolonged t_{max} and t_{lag} following oral administration.

Pharmacokinetics

Once released in the colon, mesalamine is minimally absorbed and plasma levels are similar to those found in previous studies following oral administration of doses given as 400 mg tablets. The bioequivalence between Asacol 800 (800 mg tablet) and Asacol (400 mg tablet) tablets has not been established. Following oral administration of a single, 800 mg tablet under fasting conditions, the time to peak plasma concentration (t_{max}) is approximately 10 hours while the terminal elimination half-life ($t1/2_{elm}$) is 12 to 19 hours for both mesalamine and its metabolite, N-acetyl-5-ASA.

Approximately 20% of the administered dose is absorbed systemically; the remainder is available for therapeutic activity in the colon and excretion in the feces. The extent of systemic exposure to 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-ASA.

Table 2 presents the mean pharmacokinetic parameters of 5-ASA and N-acetyl-5-ASA (N-Ac-5-ASA) following single and multiple dosing of Asacol 800 (800 mg tablet) in healthy subjects.

Table 2 Summary of mean pharmacokinetic parameters of 5-ASA and N-Ac-5-ASA following single and multiple dosing in healthy subjects

Mean Pharmacokinetic Parameters of 5-ASA		
Parameter	Single Dose (1 x 800 mg)	Multiple Dose (4.8 g/day x 6 Days)
AUC_{tlast} (ng•h/mL)	3449.2	-
AUC (ng•h/mL)	3548.2	20282.0[a]
C_{max} (ng/mL)	354.03	4972.1
t_{max} (h)	9.61	2.63
t_{lag} (h)	6.20	-
$t_{1/2,Z}$ (h)	13.41	11.89

$\%A_e$ (%)	0.21	9.28
Mean Pharmacokinetic Parameters of N-Ac-5-ASA		
Parameter	Single Dose (1 x 800 mg)	Multiple Dose (4.8 g/day x 6 Days)
AUC_{tlast} (ng•h/mL)	19900.8	-
AUC (ng•h/mL)	22034.2	24864.0[a]
C_{max} (ng/mL)	1028.68	4614.78
t_{max} (h)	11.13	3.13
t_{lag} (h)	5.39	-
$t_{1/2,Z}$ (h)	13.62	19.56
$\%A_e$ (%)	12.04	19.01
AUC_{tlast} is the area under the plasma concentration-time curve from time zero to the last quantifiable concentration; AUC is the area under the plasma concentration-time curve from time zero to infinity; C_{max} is the maximum plasma concentration; t_{max} is the time at which C_{max} is observed; t_{lag} is the lag time before the onset of drug absorption; $t_{1/2,Z}$ is the terminal exponential half-life; $\%A_e$ is the percentage of dose excreted in urine.		
[a] AUCτ is the area under the plasma concentration-time curve over a dosing interval.		

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITIONS AND PACKAGING

Asacol 800 (800 mg tablet) tablets are available for oral administration as red-brown, capsule-shaped, enteric coated tablets, printed in black ink with “WC 800”.

Each red-brown capsule-shaped enteric coated tablet of Asacol 800 (800 mg tablet) contains 800 mg mesalamine. Asacol 800 (800 mg tablet) colon-targeted tablets are coated with a special acrylic-based resin, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, which dissolves at pH 7 or greater, that delays release of the mesalamine until the tablets reach the terminal ileum. A second enteric coating which begins to dissolve earlier in the gastrointestinal tract is added after the Eudragit®-S. The outer coating consists of a combination of Eudragit®-S and another acrylic-based resin, Eudragit®-L {methacrylic acid copolymer Type A (USP)}.

Inactive ingredients include colloidal silicon dioxide, dibutyl phthalate, edible black ink (ammonium hydroxide, n-butyl alcohol, shellac glaze [modified] in SD-45, propylene glycol, synthetic black iron oxide), iron oxide red, iron oxide yellow, lactose, magnesium stearate, Eudragit®-L {methacrylic acid copolymer Type A (USP)}, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, polyethylene glycol, polyvinylpyrrolidone, sodium starch glycolate, and talc.

Asacol 800 (800 mg tablet) colon-targeted tablets are supplied in bottles of 180 tablets each.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

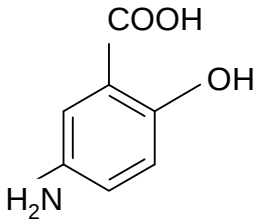
Drug Substance

Proper name: mesalamine or 5- aminosalicylic acid

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

Molecular formula and molecular mass: $C_7H_7NO_3$ Molecular Weight 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: $pK_1 = 2.74$, $pK_2 = 5.80$.

CLINICAL TRIALS

Study demographics and trial design

In the pivotal double-blind, randomized, multiple-site, controlled study in newly and previously diagnosed patients who were experiencing a flare-up of mildly to moderately active ulcerative colitis, patients were randomly assigned to receive either 2.4 g/day (Asacol 400 mg tablet) or 4.8 g/day (Asacol 800 (800 mg tablet)) for 6 weeks. A total of 301 patients were randomized to the treatment groups. In this study, a large subgroup (n = 180) of patients with moderately active ulcerative colitis was identified using the predefined stratum of baseline disease severity. Additional analyses looking at the primary, secondary and tertiary efficacy endpoints were performed in this subgroup of patients. The data from these analyses supports the efficacy of Asacol 800 (800 mg tablet) at 4.8 g/day in moderately active ulcerative colitis patients.

In the pivotal clinical trial with Asacol 800 (800 mg tablet), moderately active ulcerative colitis was determined by a Physician Global Assessment (PGA) which included clinical and endoscopic evaluations scored as a 2 on a 0 (normal) to 3 (severe) scale.

The baseline demographic characteristics for the moderately active ulcerative colitis patients are presented in Table 1.

Table 1 Summary of baseline demographic characteristics for patients with moderately active ulcerative colitis

Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
2.4 g/day (400 mg tablets orally for 6 weeks)	n=96	43.0 (18-74)	45.8% M 54.2% F
4.8 g/day (800 mg tablets orally for 6 weeks)	n=84	45.4 (20-76)	47.6% M 52.4% F

There were no statistically significant differences for any baseline demographic or anthropometric characteristic, or history of ulcerative colitis between patients with moderately active ulcerative colitis enrolled into the two treatment groups. With respect to baseline disease state characteristics, patients in the two treatment groups were not statistically different except for stool frequency scores in which more patients in the 4.8 g/day group had slightly higher stool frequency scores.

Patients enrolled into the study presented with either proctitis, proctosigmoiditis, left-sided colitis, or pancolitis and the length of disease ranged from less than one year to greater than 10 years.

In another double-blind, randomized, multiple-site, controlled study (Study 2) in newly and previously diagnosed patients who were experiencing a flare up of moderately active ulcerative colitis, patients were randomly assigned to receive either 2.4 g/day (Asacol 400 mg tablet) or 4.8 g/day (Asacol 800 (800 mg tablet)) for 6 weeks. A total of 386 patients were randomly assigned to treatment groups; 268 with moderate disease. The two moderately active ulcerative colitis treatment groups were comparable with respect to baseline demographic, disease history, and disease severity characteristics. Results from this study support the efficacy of Asacol 800 (800 mg tablet) at 4.8 g/day in moderately active ulcerative colitis patients.

Study Results

In both studies, the percentage of patients with moderately active ulcerative colitis who were classified as a treatment success after 6 weeks of therapy based on the intent-to-treat study population are presented in Table 2.

Table 2
Summary of Treatment Outcomes at Week 6
(Intent-to-treat Population With Moderate Disease [PGA = 2] at Baseline)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 223) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 200) n (%)	p-value (b)
Pivotal Study			
Treatment Success (a)	53 (57.0%)	55 (72.4%)	0.0384
Treatment Failure	40 (43.0%)	21 (27.6%)	
Study 2			
Treatment Success (a)	77 (59.2%)	89 (71.8%)	0.0357
Treatment Failure	53 (40.8%)	35 (28.2%)	
Pooled			
Treatment Success (a)	130 (58.3%)	144 (72.0%)	0.0034
Treatment Failure	93 (41.7%)	56 (28.0%)	

N = number of patients in treatment group (pooled) with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome
(a) Treatment success was defined as improvement from baseline at Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments. Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved), 2) worsening of any clinical assessments at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.
(b) 4.8 g/day compared to 2.4 g/day, from Chi-square test for 2000082 and 2000083, and stratified by protocol using the Cochran-Mantel-Haenszel test for pooled analysis.

The results of these studies for moderately active disease patients are consistent with those of a previous trial, in which the majority of patients were moderate disease patients (77%), where 4.8 g/day was administered using Asacol 400 mg tablets and 74% of patients were classified as treatment success. The findings in the Asacol 800 (800 mg tablet) studies are consistent with the fact that a higher dose of mesalamine shows greater efficacy in patients with more severe disease. Demonstrated efficacy of the Asacol 800 (800 mg tablet) tablet, administered at 4.8 g/day in the population of patients with moderately active disease, provides this population with an alternate formulation allowing daily ingestion of fewer tablets.

<u>Physician's Global Assessment and Individual Symptom and Sigmoidoscopy Scores at Weeks 3 and 6</u>

The percentage of patients whose individual clinical assessments (stool frequency score, rectal bleeding score, and PFA score), sigmoidoscopy score, and PGA score improved from baseline at Weeks 3 and 6 from both studies (pooled data) are presented in Table 3.

Table 3
Distribution of Treatment Improvement for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Patients with Moderate Disease [PGA = 2] at Baseline)

Parameter	Visit	2.4 g/day Asacol (400 mg Tablet) (N = 223) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 200) n (%)
PGA	Week 3	122 (63.5%)	130 (71.8%)
	Week 6	139 (73.2%)	152 (84.9%)*
Stool Frequency	Week 3	107 (59.4%)	112 (64.7%)
	Week 6	126 (70.8%)	126 (75.4%)
Rectal Bleeding	Week 3	110 (65.5%)	128 (74.4%)
	Week 6	130 (76.5%)	137 (81.5%)
PFA	Week 3	100 (62.5%)	90 (58.8%)
	Week 6	114 (70.8%)	108 (72.0%)
Sigmoidoscopy	Week 3	110 (57.3%)	111 (61.3%)
	Week 6	129 (67.9%)	140 (78.2%)*

Patients with no treatment outcome at Week 6 were excluded from this analysis. For patients who have a baseline score but have no score at visit, the improvement status cannot be determined. These patients were also excluded from this analysis.
* = Between-treatment difference is statistically significant ($p<0.05$) using the Cochran-Mantel-Haenszel test stratified by protocol.
N = number of patients in treatment group with treatment outcome at Week 6
n(%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome in specified parameter

In both studies, more patients showed improvement on 4.8 g/day compared to 2.4 g/day across the clinical assessments (stool frequency, rectal bleeding, sigmoidoscopy and PGA). From pooled results, 4.8 g/day showed statistically significant superiority in the sigmoidoscopy and PGA scores at 6 weeks.

Results from both studies (pooled data) demonstrate that the median time to resolution of increased stool frequency, rectal bleeding, and the composite of both symptoms were shorter for the 4.8 g/day group than for the 2.4 g/day group. In addition, the difference between groups was statistically significant for the median time to resolution of rectal bleeding (9 days for 4.8 g/day group vs 16 days for 2.4 g/day group) and the composite of both symptoms (19 days for 4.8 g/day group vs 29 days for 2.4 g/day group), favouring the 4.8 g/day group.

Quality-of-life Scores

The quality-of-life scores derived from the Inflammatory Bowel Disease Questionnaire (IBDQ) at Weeks 3 and 6 from both studies (pooled data) are presented in Table 4.

Table 4
Mean Change from baseline in Inflammatory Bowel Disease Questionnaire Scores at Weeks 3 and 6
(Patients with Moderate Disease [PGA = 2] at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 235)		4.8 g/day Asacol (800 mg Tablet) (N = 213)	
Category	n	Mean	n	Mean
Total				
Week 3	189	30.1*	183	33.7*
Week 6	183	42.6*	176	45.0*
Exit	212	36.4*	193	40.2*
Bowel				
Week 3	190	11.4*	182	13.1*
Week 6	183	16.4*	176	17.4*
Exit	212	14.4*	193	15.6*
Systemic				
Week 3	191	4.3*	184	5.1*
Week 6	185	6.1*	177	6.8*
Exit	214	5.2*	194	5.9*
Emotional				
Week 3	187	9.9*	181	11.1*
Week 6	182	13.9*	175	14.8*
Exit	211	11.8*	192	13.2*
Social				
Week 3	191	4.2*	182	4.6*
Week 6	186	5.9*	176	5.9*
Exit	215	4.7*	193	5.3*

Exit is the Week 6 visit for those who completed the study and the withdrawal visit for those who dropped out.
N = number of patients in treatment group with treatment outcome at Week 6
n = number of patients from which statistics were calculated.
* = Change from baseline using t-test is statistically significant ($p<0.0001$).

Quality of life pooled data from both studies using the IBDQ showed statistically significant improvement from baseline in both treatment groups at both week 3 and week 6. No statistically significant differences were seen between treatment groups; however, there was a trend for scores to favour 4.8 g/day dosing over 2.4 g/day dosing.

DETAILED PHARMACOLOGY

Mesalamine release from Asacol 800 (800 mg tablet) is delayed until the terminal ileum as reflected by the time to peak plasma concentration (t_{max}) that is approximately 10 hours or greater for mesalamine and its metabolite, N-acetyl-5-ASA. The terminal elimination half-life ($t1/2_{elm}$) is 12 to 19 hours for both mesalamine and N-acetyl-5-ASA.

Human studies conducted using radiological and serum markers, with the 400 mg tablets, showed that the Asacol (400 mg tablet) coating delayed release of mesalamine until the terminal ileum was reached. Other studies with mesalamine compared its 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. Results indicated that 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-ASA.

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 (400 mg tablet) 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

[Pr] Asacol® 800
Mesalamine Delayed-Release Tablets, Mfr. Std.

This leaflet is part III of a three-part "Product Monograph" published when Asacol 800 (800 mg tablet) 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 800 (800 mg tablet). Consult your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Asacol 800 (800 mg tablet) is used for the treatment of moderately active ulcerative colitis. Ulcerative colitis involves chronic inflammation of the inner lining of the colon and rectum.

What it does:
Asacol 800 (800 mg tablet) has a special outer coating that is designed to remain intact, to protect the active ingredient, mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), until it reaches the terminal ileum and colon where the tablet releases its contents. The active ingredient mesalamine is believed to reduce inflammation right at the site, where the medication is needed.

When it should not be used:
Asacol 800 (800 mg tablet) 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®)
- If you have severe liver problems
- If you have severe kidney problems.
- You have an existing 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:
Each red-brown capsule-shaped enteric coated tablet of Asacol 800 (800 mg tablet) contains 800 mg mesalamine, otherwise known as 5-aminosalicylic acid or 5-ASA.

What the important nonmedicinal ingredients are:
Asacol 800 (800 mg tablet) colon-targeted tablets are coated with a special acrylic-based resin, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, that delays release of the mesalamine until the tablets reach the terminal ileum.

Inactive ingredients include colloidal silicon dioxide, dibutyl phthalate, edible black ink (ammonium hydroxide, n-butyl alcohol, shellac glaze [modified] in SD-45, propylene glycol, synthetic black iron oxide), iron oxide red, iron oxide yellow, lactose, magnesium stearate, Eudragit®-L {methacrylic acid copolymer Type A (USP)}, Eudragit®-S {methacrylic acid copolymer Type B (USP)}, polyethylene glycol, polyvinylpyrrolidone, sodium starch glycolate, and talc.

What dosage form it comes in:
Asacol 800 (800 mg tablet) tablets are available for oral administration as red-brown, capsule-shaped, enteric coated tablets, printed in black ink with "WC 800".

Asacol 800 (800 mg tablet) colon-targeted tablets are supplied in bottles of 180 tablets each.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
If you have an allergic reaction to Asacol 800 (800 mg tablet), 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 800 (800 mg tablet). If you have a history of kidney problems, you should tell your doctor before using Asacol 800 (800 mg tablet), as it may worsen your kidney condition. Your doctor may require certain tests to check your kidney function before starting Asacol 800 (800 mg tablet) therapy and periodically while you continue Asacol 800 (800 mg tablet) therapy.

Some patients who have experienced an allergic reaction to sulfasalazine may have a similar reaction to Asacol 800 (800 mg tablet) or to other products that contain, or are converted to, mesalamine. Asacol 800 (800 mg tablet) 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 800.

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 800 (800 mg tablet) talk to your doctor or pharmacist if:
- You have any liver or kidney problems.
- 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 800 (800 mg tablet) tablet from reaching the colon as quickly as it normally would.

- You are pregnant, become pregnant, or are a nursing mother. Small amounts of 5-aminosalicyclic acid and its metabolite have been found in human breast milk. Dibutyl phthalate (DBP) an inactive ingredient in the enteric coating of Asacol 800 (800 mg tablet), and its primary metabolite mono-butyl phthalate (MBP) are also excreted into human milk. Caution should be taken when using Asacol 800 (800 mg tablet) while you are nursing. Discuss with your doctor.

INTERACTIONS WITH THIS MEDICATION

There has been no specific drug interaction studies performed with Asacol 800 (800 mg tablet). In addition, interactions with herbal products or laboratory tests have not been established. If you are on other prescription medications or on over-the-counter products, including herbal supplements, or are undergoing a laboratory test, please consult your doctor or pharmacist.

Asacol 800 (800 mg tablet) can be taken with or without food.

PROPER USE OF THIS MEDICATION

Usual dose:

For the treatment of moderately active ulcerative colitis: The usual daily adult dose is 6 Asacol 800 (800 mg tablet) tablets, taken orally in divided doses. Asacol 800 (800 mg tablet) may be given with or without food.

Ulcerative colitis rarely disappears completely. Abrupt discontinuation of medication is not recommended, as it may trigger the symptoms to appear again. It is important to closely follow your doctor's dosage instructions, to help reduce the risk of symptoms re-appearing.

When taking Asacol 800 (800 mg tablet), 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 800 (800 mg tablet) 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 800 (800 mg tablet) 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 include worsening of ulcerative colitis symptoms, abnormal liver function tests and rash.

Inform your doctor, if you experience any of the following symptoms while taking Asacol 800 (800 mg tablet): worsening of your ulcerative colitis symptoms, fever, rash, chest pain or stomach pain, or difficulty breathing.

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		✓	
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**		✓	

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**
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 is not a complete list of side effects. For any other side effects or health concerns while taking Asacol 800 (800 mg tablet), contact your doctor or pharmacist.

HOW TO STORE IT

Asacol 800 (800 mg tablet) should be stored at controlled room temperature (15°C – 30°C).

Keep out of reach of children.

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.asacol.ca

This document plus the full product monograph, prepared for health professionals is available by contacting the sponsor, Warner Chilcott Canada Co. at: 1-800-565-0814

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