

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ASACOL safely and effectively. See full prescribing information for ASACOL.

ASACOL (mesalamine) delayed-release tablets, for oral use

Initial U.S. Approval: 1987

INDICATIONS AND USAGE

Asacol is an aminosalicylate indicated for:

- Treatment of mildly to moderately active ulcerative colitis (UC) in patients 5 years of age and older (1.1).
- Maintenance of remission of mildly to moderately active UC adults (1.2)

DOSAGE AND ADMINISTRATION

Important Administration Instructions:

- Evaluate renal function prior to initiation of Asacol and periodically while on therapy (2.1, 5.1)
- Two Asacol 400 mg tablets are not interchangeable or substitutable with one mesalamine delayed-release 800 mg tablet (2.1)

Treatment of mildly to moderately active UC (2.2):

- Adults: 800 mg (two 400 mg tablets) three times daily for 6 weeks
- Pediatric Patients 5 years or older: Total daily dosage is weight-based up to a maximum of 2.4 grams/day divided into two daily doses (see Table 1)

Maintenance of remission of mildly to moderately active UC (2.3)

- Adults: 1.6 grams (four 400 mg tablets) daily in two to four divided doses.

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets: 400 mg (3)

CONTRAINDICATIONS

Known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Asacol tablets (4, 5.3)

WARNINGS AND PRECAUTIONS

- **Renal Impairment:** Evaluate the risks and benefits in patients with known renal impairment or taking nephrotoxic drugs; monitor renal function (5.1, 7.1, 8.6, 13.2)
- **Mesalamine-induced Acute Intolerance Syndrome:** Symptoms may be difficult to distinguish from a UC exacerbation; monitor for worsening symptoms; discontinue if acute intolerance syndrome suspected (5.2)
- **Hypersensitivity Reactions, including Myocarditis and Pericarditis:** Evaluate patients immediately and discontinue if a hypersensitivity reaction is suspected (5.3)
- **Hepatic Failure:** Evaluate the risks and benefits in patients with known liver impairment (5.4)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) for the treatment of mild to moderate UC are (6.1):

- **Adults:** eructation, abdominal pain, constipation, dizziness, rhinitis, back pain, and rash
- **Pediatric Patients 5 to 17 years of age:** nasopharyngitis, headache, abdominal pain, dizziness, sinusitis, rash, cough and diarrhea

To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- **Nephrotoxic Agents including NSAIDs:** Increased risk of nephrotoxicity; monitor for changes in renal function and mesalamine-related adverse reactions. (7.1)
- **Azathioprine or 6-Mercaptopurine:** Increased risk of blood disorders; monitor complete blood cell counts and platelet counts (7.2)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Contains dibutyl phthalate; may cause fetal harm (8.1)
- **Geriatric Patients:** Increased risk of blood dyscrasias; monitor complete blood cell counts and platelet counts (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE
1.1	Treatment of Mildly to Moderately Active Ulcerative Colitis
1.2	Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis
2	DOSAGE AND ADMINISTRATION
2.1	Important Administration Instructions
2.2	Dosage for Treatment of Mildly to Moderately Active Ulcerative Colitis
2.3	Dosage for Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Renal Impairment
5.2	Mesalamine-Induced Acute Intolerance Syndrome
5.3	Hypersensitivity Reactions
5.4	Hepatic Failure
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Postmarketing Experience
7	DRUG INTERACTIONS
7.1	Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs
7.2	Azathioprine or 6-Mercaptopurine

8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Lactation
8.4	Pediatric Use
8.5	Geriatric Use
8.6	Renal Impairment
10	OVERDOSAGE
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2	Animal Toxicology and/or Pharmacology
14	CLINICAL STUDIES
14.1	Treatment of Mildly to Moderately Active Ulcerative Colitis
14.2	Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis
15	REFERENCES
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

Asacol[®] is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

1.2 Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis

Asacol is indicated for the maintenance of remission of mildly to moderately active ulcerative colitis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Two Asacol 400 mg tablets are not interchangeable or substitutable with one mesalamine delayed-release 800 mg tablet.
- Evaluate renal function prior to initiation of Asacol
- Take Asacol tablets with or without food.
- Swallow Asacol tablets whole. Do not cut, break or chew the tablets.
- Intact, partially intact, and/or tablet shells have been reported in the stool; Instruct patients to contact their physician if this occurs repeatedly.
- Protect Asacol tablets from moisture. Close the container tightly and to leave any desiccant pouches present in the bottle along with the tablets.

2.2 Dosage for Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults

For adults, the recommended dosage of Asacol is 800 mg (two 400 mg tablets) three times daily (total daily dosage of 2.4 grams) for a duration of 6 weeks.

Pediatrics

For pediatric patients 5 years of age and older, the recommended total daily dosage of Asacol is weight-based (up to maximum of 2.4 grams/day) divided into two daily doses for a duration of 6 weeks (see [Table 1](#)).

Table 1. Pediatric Dosage by Weight

Weight Group (kg)	Daily Dosage (mg/kg/day)	Maximum Daily Dosage (grams/day)	Morning Dosage	Afternoon Dosage
17 to <33	36 to 71	1.2	two 400 mg tablets	one 400 mg tablet
33 to <54	37 to 61	2	three 400 mg tablets	two 400 mg tablets
54 to 90	27 to 44	2.4	three 400 mg tablets	three 400 mg tablets

2.3 Dosage for Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis

For adults the recommended dosage of Asacol is 1.6 grams (four 400 mg tablets) daily in two to four divided doses.

3 DOSAGE FORMS AND STRENGTHS

Asacol (mesalamine) Delayed-Release Tablets: 400 mg (red-brown, capsule-shaped and imprinted with “0752 DR” in black).

4 CONTRAINDICATIONS

Asacol is contraindicated in patients with known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Asacol [see *Warnings and Precautions* (5.3), *Adverse Reactions* (6.2), and *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure, has been reported in patients taking products such as Asacol that contain mesalamine or are converted to mesalamine [see *Adverse Reactions* (6.2)].

Evaluate renal function prior to initiation of Asacol and periodically while on therapy.

Evaluate the risks and benefits of using Asacol in patients with known renal impairment or history of renal disease or taking concomitant nephrotoxic drugs [see *Drug Interactions* (7.1), *Use in Specific Populations* (8.6) and *Nonclinical Toxicology* (13.2)].

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of controlled clinical trials of mesalamine or sulfasalazine.

Symptoms include cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with Asacol.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to Asacol or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue Asacol if an alternative etiology for the signs or symptoms cannot be established.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Evaluate the risks and benefits of using Asacol in patients with known liver impairment.

6 ADVERSE REACTIONS

The most serious adverse reactions seen in Asacol clinical trials or with other products that contain mesalamine or are metabolized to mesalamine are:

- Renal Impairment [*see Warnings and Precautions (5.1)*]
- Mesalamine-Induced Acute Intolerance Syndrome [*see Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.3)*]
- Hepatic Failure [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

In total, Asacol tablets have been evaluated in 2,690 patients with ulcerative colitis in controlled and open-label trials.

Clinical studies supporting Asacol use for the treatment of mildly to moderately active ulcerative colitis included two 6-week, placebo-controlled, randomized, double-blind studies in adults with mildly to moderately active ulcerative colitis (Studies 1 and 2), and one 6-week, randomized, double-blind, study of 2 dosage levels in children with mildly to moderately active ulcerative colitis (Study 3). Clinical studies supporting the use of Asacol tablets in the maintenance of remission of mildly to moderately active ulcerative colitis included a 6-month, randomized, double-blind, placebo-controlled, multi-center study (Study 4) and four active-controlled maintenance trials comparing Asacol tablets with sulfasalazine. Asacol has been evaluated in 427 adults and 82 children with ulcerative colitis in these controlled studies.

Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults

In a 6-week placebo-controlled clinical study (Study 1) involving 105 patients, 53 of whom were randomized to Asacol 2.4 grams/day [see *Clinical Studies (14.1)*], 4% of the Asacol-treated patients in 2.4 grams/day group discontinued therapy because of adverse reactions as compared to 0% of the placebo-treated patients. The average age of patients was 41 years and 49% of patients were male. Adverse reactions leading to withdrawal from Asacol included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache.

The most common adverse reactions in patients treated with Asacol 2.4 grams/day in Study 1 are listed in [Table 2](#) below.

Table 2. Most Common Adverse Reactions Reported in Study 1 for the Treatment of Mildly to Moderately Active Ulcerative Colitis in Adults*

Adverse Reaction	% of Patients with Adverse Reactions	
	Asacol 2.4 grams/day	Placebo
	(n = 53)	(n = 52)
Eructation	26	19
Abdominal pain	21	12
Constipation	11	0
Dizziness	9	8
Rhinitis	8	6
Back pain	6	4
Rash	6	4
Dyspepsia	4	0
Flu syndrome	4	2

* At Least 2% of Patients in the Asacol Group and at a Rate Greater than Placebo

Pediatric Patients 5 to 17 Years Old

A randomized, double-blind, 6-week study of 2 dosage levels of Asacol (Study 3) was conducted in 82 pediatric patients 5 to 17 years of age with mildly to moderately active ulcerative colitis. All patients were divided by body weight category (17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg) and randomly assigned to receive a low dosage (1.2, 2, and 2.4 grams/day for the respective body weight category) or a high dosage (2, 3.6, and 4.8 grams/day).

The high dosage regimen is not recommended because it was not found to be more effective than the recommended low dosage regimen [see *Dosage and Administration (2.1)* and *Clinical Studies (14.1)*].

Duration of exposure to Asacol among the 82 patients in the study ranged from 12 to 50 days (mean of 40 days in each dosage group). The majority (88%) of patients in each group were treated for more than 5 weeks. [Table 3](#) provides a summary of the specific reported adverse reactions.

Table 3. Adverse Reactions \geq 5% Reported in Study 3 for the Treatment of Mildly to Moderately Active Ulcerative Colitis in Pediatric Patients*

Adverse Reaction	% of Patients with Adverse Reactions	
	Asacol Low Dosage	Asacol High Dosage
	(n=41)	(n=41)
Nasopharyngitis	15	12
Headache	10	5
Abdominal pain	10	2
Dizziness	7	2
Sinusitis	7	0
Rash	5	5
Cough	5	0
Diarrhea	5	0
Fatigue	2	10
Pyrexia	0	7
Increased Lipase	0	5
Low Dosage = Asacol 1.2 to 2.4 grams/day; High Dosage = Asacol 2.0 to 4.8 grams/day. Dosage was dependent on body weight.		
Adverse Reactions reported at the 1-week telephone follow-up visit are included.		

* At Least 5% of Patients in the low dosage or high dosage group

Twelve percent of the patients in the low dosage group (5 patients) and 2% of the patients in the high dosage group (1 patient) had serious adverse reactions. The serious adverse reactions consisted of sinusitis, adenovirus infection, and pancreatitis in one patient each in the low dosage group. Abdominal pain and decreased body mass index occurred in one patient and bloody diarrhea and sclerosing cholangitis also occurred in one patient in the low dosage group. Anemia and syncope occurred in one patient in the high dosage group.

Five patients were withdrawn from the study due to adverse reactions: 3 (7%) in the low dosage group (1 patient each with adenovirus infection, sclerosing cholangitis, and pancreatitis) and 2 patients (5%) in the high dosage group (1 patient with increased amylase and increased lipase, and 1 patient with upper abdominal pain).

In general, the nature and severity of reactions in the pediatric population was similar to those reported in adult populations of patients with ulcerative colitis.

Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis

Clinical studies supporting the use of Asacol tablets in the maintenance of remission of mildly to moderately active ulcerative colitis in adults included a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration in 264 patients (Study 4 [see *Clinical Studies (14.2)*]).

In Study 4, a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration, 87 patients were randomized to receive Asacol 1.6 grams/day compared to 87 patients randomized to placebo. The average age of patients in Study 4 was 42 years and 55 % of patients were male. Adverse reactions leading to study withdrawal in patients using Asacol included (each in one patient): anxiety, stomatitis and asthenia.

In addition to the adverse reactions listed in [Table 2](#), the following occurred at a frequency of 2% or greater in patients who received Asacol in Study 4: abdominal enlargement, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, nervousness, paresthesia, hemorrhoids, tenesmus, urinary frequency, and vision abnormalities.

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving Asacol, the adverse reactions listed below have been identified during post-approval use of Asacol and other mesalamine-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome, drug fever.

Cardiovascular: Pericarditis, myocarditis [*see Warnings and Precautions (5.3)*].

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer, bloody diarrhea.

Hematologic: Agranulocytosis aplastic anemia, thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy, transverse myelitis, Guillain-Barré syndrome.

Renal: Renal failure, interstitial nephritis, minimal change nephropathy [*see Warnings and Precautions (5.1)*].

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

Skin: Alopecia, psoriasis, pyoderma gangrenosus, dry skin, erythema nodosum, urticaria.

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Dysuria, urinary urgency, hematuria, epididymitis, menorrhagia, reversible oligospermia.

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

7 DRUG INTERACTIONS

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

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 [*see Warnings and Precautions (5.1)*].

7.2 Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood disorders. If concomitant use of Asacol and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk. No fetal harm was observed in animal reproduction studies of mesalamine in rats and rabbits at oral doses approximately 1.9 times (rat) and 3.9 times (rabbit) the recommended human dose [*see Data*]. However, dibutyl phthalate (DBP) is an inactive ingredient in Asacol's enteric coating, and in animal studies in rats at doses greater than 190 times the human dose, maternal DBP was associated with external and skeletal malformations and adverse effects on the reproductive system of male offspring. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired fertility or harm to the fetus. These mesalamine doses were about 1.9 times (rat) and 3.9 times (rabbit) the recommended human dose, based on body surface area.

DBP is an inactive ingredient in Asacol's enteric coating. The human daily intake of DBP from the maximum recommended dose of Asacol tablets is about 21 mg. Published reports in rats show that male rat offspring exposed in utero to DBP (greater than or equal to 100 mg/kg/day, approximately 39 times the human dose based on body surface area), display reproductive system aberrations compatible with disruption of androgenic dependent development. The clinical significance of this finding in rats is unknown. At higher dosages (greater than or equal to 500 mg/kg/day, approximately 194 times the human dose based on body surface area), additional effects, including cryptorchidism, hypospadias, atrophy or agenesis of sex accessory organs, testicular injury, reduced daily sperm production, permanent retention of nipples, and decreased anogenital distance are noted. Female offspring are unaffected. High

doses of DBP, administered to pregnant rats was associated with increased incidences of developmental abnormalities, such as cleft palate (greater than or equal to 630 mg/kg/day, about 244 times the human dose, based on body surface area) and skeletal abnormalities (greater than or equal to 750 mg/kg/day, about 290 times the human dose based on body surface area) in the offspring.

8.2 Lactation

Risk Summary

Mesalamine and its N-acetyl metabolite are present in human milk in undetectable to small amounts [see *Data*]. There are limited reports of diarrhea in breastfed infants. There is no information on the effects of the drug on milk production. Additionally, DBP, an inactive ingredient in the enteric coating of Asacol tablets, and its primary metabolite mono-butyl phthalate (MBP) are present in human milk, but the clinical significance is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Asacol and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for diarrhea.

Data

Human Data

In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 3 g daily. The concentration of mesalamine in milk ranged from non-detectable to 0.11 mg/L. The concentration of the N-acetyl-5-aminosalicylic acid metabolite ranged from 5 to 18.1 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 to 0.017 mg/kg/day of mesalamine and 0.75 to 2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid.

8.4 Pediatric Use

The safety and effectiveness of Asacol in pediatric patients 5 to 17 years of age for treatment of mildly to moderately active ulcerative colitis have been established over a 6-week period. Use of Asacol in these age groups is supported by evidence from adequate and well controlled studies of Asacol in adults and a single study in 82 pediatric patients 5 to 17 years of age [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14.1)].

The safety and effectiveness of Asacol for the maintenance of remission of mildly to moderately active ulcerative colitis in pediatric patients have not been established. Efficacy was not demonstrated in a randomized, double-blind 26-week trial of two dosage levels for maintenance of remission of mildly to moderately active ulcerative colitis initiated in 39 patients aged 5 to 17 years. Possible factors contributing to this outcome included the dose range studied and premature termination of the trial.

8.5 Geriatric Use

Clinical studies of Asacol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Reports from uncontrolled clinical studies and postmarketing experience suggest a higher incidence of blood dyscrasias (agranulocytosis, neutropenia, pancytopenia) in patients receiving Asacol who are 65 years or older compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with Asacol.

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Asacol [see Use in Specific Populations (8.6)].

8.6 Renal Impairment

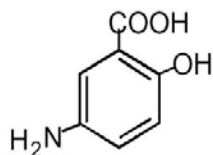
Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on Asacol therapy. Monitor patients with known renal impairment or history of renal disease or taking nephrotoxic drugs for decreased renal function and mesalamine-related adverse reactions [see Warnings and Precautions (5.1), Drug Interactions (7.1) and Adverse Reactions (6.2)].

10 OVERDOSAGE

There is no specific antidote for mesalamine overdose and treatment for suspected acute severe toxicity with Asacol should be symptomatic and supportive. This may include prevention of further gastrointestinal tract absorption, correction of fluid electrolyte imbalance, and maintenance of adequate renal function. Asacol is a pH dependent delayed-release product and this factor should be considered when treating a suspected overdose.

11 DESCRIPTION

Each Asacol (mesalamine) delayed-release tablet for oral administration contains 400 mg of mesalamine, an aminosalicylate. Asacol (mesalamine) Delayed-Release Tablets contain acrylic based resin, Eudragit S (methacrylic acid and methyl methacrylate copolymer), which dissolves at pH 7 or greater and releases mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA) has the chemical name 5-amino-2-hydroxybenzoic acid. Its structural formula is:



Molecular Weight: 153.1
Molecular Formula: C₇H₇NO₃

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, dibutyl phthalate, edible black ink, ferric oxide red, ferric oxide yellow, lactose monohydrate, magnesium stearate, methacrylic acid and methyl methacrylate copolymer (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, that is, prostanoids, and through the lipoxygenase pathways, that is, leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic ulcerative colitis, and it is possible that mesalamine

diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

12.3 Pharmacokinetics

Absorption

Approximately 28% of mesalamine in Asacol tablets is absorbed after oral ingestion. Absorption of mesalamine is similar in fasted and fed subjects. The T_{max} for mesalamine and its metabolite, is usually delayed, reflecting the delayed-release, and ranges from 4 to 16 hours.

Elimination

Metabolism

The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver to N-acetyl-5-aminosalicylic acid.

Excretion

Absorbed mesalamine is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid. Unabsorbed mesalamine is excreted in feces.

After intravenous administration, the elimination half-life of mesalamine is reported to be approximately 40 minutes. After oral dosing, the terminal $t_{1/2}$ values for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 hours, but are variable, ranging from 2 to 15 hours. There is a large inter-subject and intra-subject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination half-lives following administration of Asacol.

Specific Populations

Pediatric Patients

In a dose-ranging pharmacokinetic study evaluating 30, 60 and 90 mg/kg/day doses of Asacol administered twice daily for four weeks, the mean average concentration (C_{avg}) values of mesalamine in pediatric ulcerative colitis patients ranged from approximately 400 ng/mL to 2100 ng/mL based on data from all dose levels.

In a study in pediatric ulcerative colitis patients (Study 3), mean plasma concentrations of mesalamine (based on sparse sampling) were 820 to 988 ng/mL at the low dosage level (that is, 1.2, 2 or 2.4 grams/day based on body weight strata of 17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg, respectively).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mesalamine was not carcinogenic at dietary dosages of up to 480 mg/kg/day in rats and 2000 mg/kg/day in mice, which are about 2.9 and 6.1 times of the maximum recommended maintenance dosage of Asacol of 1.6 grams/day or 26.7 mg/kg/day, based on 60 kg body weight, respectively, based on body surface area.

Mutagenesis

Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes.

Impairment of Fertility

Mesalamine, at oral dosages up to 480 mg/kg/day (about 1.9 times the recommended human treatment dosage on a body surface area basis), was found to have no effect on fertility or reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. (In the following, comparisons of animal dosing to recommended human dosing are based on body surface area and a 2.4 grams/day dose for a 60 kg person.)

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (approximately 3 to 4 times the recommended human dose based on body surface area). Doses of 170 and 360 mg/kg/day (about 0.7 and 1.5 times the recommended human dose based on body surface area) given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia.

In mice, oral doses of 4000 mg/kg/day mesalamine (approximately 8 times the recommended human dose based on body surface area) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 8 times the recommended human dose based on body surface area) of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (1.1 times the recommended human dose based on body surface area).

14 CLINICAL STUDIES

14.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults

Two placebo-controlled studies (Studies 1 and 2) have demonstrated the efficacy of Asacol in patients with mildly to moderately active ulcerative colitis.

In one randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 weeks' duration in 158 patients (Study 1), patients received Asacol dosages of 1.6 grams/day (800 mg twice a day; n=53) and 2.4 grams/day (800 mg three times a day; n=53), compared to placebo (n=52). The scoring system for determination of treatment efficacy included assessment of stool frequency, rectal bleeding, sigmoidoscopic findings, patient's functional assessment, and physician global assessment. At the dosage of 2.4 grams/day, 21 of 43 (49%) patients using Asacol showed an improvement in sigmoidoscopic appearance of the bowel compared to 12 of 44 (27%) patients using placebo (p = 0.048). In addition, significantly more patients in the Asacol 2.4 grams/day group showed improvement in rectal bleeding and stool frequency. The 1.6 grams/day dosage regimen is not recommended because it did not produce consistent evidence of effectiveness [see *Dosage and Administration* (2.2)].

In a second randomized, double-blind, placebo-controlled clinical trial of 6 weeks' duration in 87 patients (Study 2), patients received Asacol dosages of 1.6 grams/day (400 mg four times a day; n=11) and 4.8 grams/day (1.2 g four times a day; n=38), compared to placebo four times a day (n=38). Asacol 4.8 grams/day for 6 weeks resulted in sigmoidoscopic improvement in 28 of 38 (74 %) patients compared to 10 of 38 (26 %) placebo patients (p less than 0.001). Also, more patients in the Asacol 4.8 grams/day group than the placebo group showed improvement in overall symptoms. The 4.8 grams/day dosage regimen is not recommended because greater efficacy was not demonstrated with this dosage compared to the 2.4 grams/day dosage [see *Dosage and Administration* (2.2)].

Pediatrics

The safety and effectiveness of Asacol in pediatric patients 5 to 17 years of age for treatment of mildly to moderately active ulcerative colitis are supported by evidence from adequate and well controlled studies of Asacol in adults and a single study in pediatric patients.

A randomized, double-blind, 6-week study of two dosage levels of Asacol (Study 3) was conducted in 82 pediatric patients 5 to 17 years of age with mildly or moderately active ulcerative colitis defined as a score of 10 to 55 on the Pediatric Ulcerative Colitis Activity Index (PUCAI) (which includes assessment of abdominal pain, rectal bleeding, stool consistency, number of stools per 24 hours, presence of nocturnal bowel movement and activity level, and has a total maximum score of 85; each of the subscales are scored from 0 to 10 except rectal bleeding which is scored from 0 to 30, and number of stools per 24 hours which is scored from 0 to 15) and rectal bleeding and stool frequency Mayo subscale scores of ≥ 1 (each of these subscales are scored from zero (normal) to three (most severe)).^{1,2}

All patients were divided by weight category (17 to less than 33 kg, 33 to less than 54 kg, and 54 to 90 kg) and randomly assigned to receive a low dosage (1.2, 2, and 2.4 grams/day for the respective weight category) or a high dosage (2, 3.6, and 4.8 grams/day). Doses were administered every 12 hours.

The proportion of patients who achieved success based on the Truncated Mayo Score (TM-Mayo) (based on the stool frequency and rectal bleeding subscales of the Mayo Score) and based on the PUCAI was measured after 6 weeks of treatment. Success based on TM-Mayo was defined as either partial response (improvement from baseline in stool frequency or rectal bleeding subscores with no worsening in the other) or complete response (both stool frequency and rectal bleeding subscores equal 0). Success based on PUCAI was defined as either partial response (PUCAI reduction of greater than or equal to 20 points from Baseline to Week 6 with Week 6 score greater than or equal to 10) or complete response (PUCAI less than 10 at Week 6).

There were 41 patients in the low dosage group and 41 patients in the high dosage group who received at least one dose of Asacol; 36 patients in each dosage group completed the study. Patients were considered treatment failures if they did not achieve success or dropped out due to adverse reaction or lack of efficacy.

At Week 6, 73% of the patients in the low dosage group, and 70% of the patients in the high dosage group achieved success based on the TM-Mayo; 34% of the patients in the low dosage group and 43% of the patients in the high dosage group achieved complete response. At Week 6, 56% of the patients in the low dosage group, and 55% of the patients in the high dosage group achieved success based on the PUCAI; 46% of the patients in the low dosage group and 43% of the patients in the high dosage group achieved complete response.

The high dosage regimen is not recommended because it was not more effective than the low dosage regimen [see *Dosage and Administration* (2.2)].

14.2 Maintenance of Remission of Mildly to Moderately Active Ulcerative Colitis

Adults

In a randomized, double-blind, multi-center, placebo-controlled clinical trial of 6 months' duration in 264 patients (Study 4), patients received Asacol dosages of 0.8 grams/day (400 mg twice a day; n = 90) and 1.6 grams/day (400 mg four times a day; n = 87), compared to placebo four times a day (n = 87). The proportion of patients treated with 0.8 grams/day who maintained endoscopic remission was not statistically significant compared to placebo; the 0.8 grams/day dosage regimen is not recommended [*see Dosage and Administration (2.2)*]. The number of patients using Asacol 1.6 grams/day who maintained endoscopic remission of ulcerative colitis was 61 of 87 (70%) compared with 42 of 87 (48%) of placebo patients (p = 0.005).

A pooled efficacy analysis of 4 maintenance trials compared Asacol at dosages of 0.8 to 2.8 grams/day, in divided doses ranging from twice daily to four times per day, with sulfasalazine, at dosages of 2 to 4 grams/day. Treatment success was seen in 59 of 98 (59%) patients using Asacol and 70 of 102 (69%) patients using sulfasalazine, a non-significant difference.

15 REFERENCES

1. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. *Gastroenterology*. 2007;133:423–432.
2. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N Engl J Med*. 1987;317(26):1625-9.

16 HOW SUPPLIED/STORAGE AND HANDLING

Asacol Delayed-Release Tablets: 400 mg (red-brown, capsule-shaped tablets containing 400 mg mesalamine and imprinted with “0752 DR” in black.

NDC 0430-0752-27 Bottle of 180 tablets

Store at 20° to 25° C (68° to 77° F); excursions permitted 15° to 30° C (59° to 86° F) [*See USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

Administration

- Inform patients that if they are switching from a previous oral mesalamine therapy to Asacol to discontinue their previous oral mesalamine therapy and follow the dosing instructions for Asacol. Inform patients that two Asacol 400 mg tablets cannot be substituted for one Asacol HD 800 mg tablet.
- Inform patients that Asacol tablets can be taken with or without food.
- Instruct patients to swallow the Asacol tablets whole, taking care not to break, cut, or chew the tablets, because the coating is an important part of the delayed-release formulation.

- Inform patients that intact, partially intact, and/or tablet shells have been reported in the stool. Instruct patients to contact their physician if this occurs repeatedly.
- Instruct patients to protect Asacol tablets from moisture. Instruct patients to close the container tightly and to leave any desiccant pouches present in the bottle along with the tablets.

Renal Impairment

- Inform patients that Asacol may decrease their renal function, especially if they have known renal impairment or are taking nephrotoxic drugs, and periodic monitoring of renal function will be performed while they are on therapy. Advise patients to complete all blood tests ordered by their physician.

Mesalamine-Induced Acute Intolerance Syndrome

- Instruct patients to report to their physician if they experience new or worsening symptoms of cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash.

Hypersensitivity Reactions

- Inform patients of the signs and symptoms of hypersensitivity reactions, and advise them seek immediate medical care should signs and symptoms occur.

Pregnant Women/Nursing Mothers

- Advise women who are pregnant, breastfeeding, or of childbearing potential that Asacol contains dibutyl phthalate, which was associated with malformations and adverse effects on the male reproductive system in animal studies. Dibutyl phthalate is excreted in human milk.

Hepatic Failure

- Inform patients with known liver disease of the signs and symptoms of worsening liver function and advise them to report to their physician if they experience such signs or symptoms.

Blood Disorders

- Inform elderly patients and those taking azathioprine or 6-mercaptopurine of the risk for blood disorders and the need for periodic monitoring of complete blood cell counts and platelet counts while on therapy. Advise patients to complete all blood tests ordered by their physician.

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Marketed by:

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