

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

-----RECENT MAJOR CHANGES-----

Indications and Usage (1.1) 10/2013
Dosage and Administration (2.1) 10/2013

-----INDICATIONS AND USAGE-----

Asacol is an aminosalicylate indicated for:

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

-----DOSAGE AND ADMINISTRATION-----

- Treatment of mildly to moderately active ulcerative colitis (2.1):
 - Adults: 800 mg three times daily (2.4 grams/day) for 6 weeks
 - Pediatric Patients 5 years or older: Total daily dose is weight-based up to a maximum of 2.4 grams/day (see table below); twice daily dosing

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

- Maintenance of remission of ulcerative colitis in adults: 1.6 grams daily, in divided doses (2.2)
- Instruct patients to swallow tablets whole without cutting, breaking, or chewing and to take tablets with or without food (2.3)
- Two Asacol 400 mg tablets cannot be substituted for one Asacol HD (mesalamine) delayed-release 800 mg tablet (2.3)
- Recommend that renal function be evaluated prior to initiation of Asacol (2.4, 5.1)

-----DOSAGE FORMS AND STRENGTHS-----

Delayed-release tablets: 400 mg (3)

-----CONTRAINDICATIONS-----

Patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Asacol tablets (4, 5.3)

-----WARNINGS AND PRECAUTIONS-----

- *Development of Renal Impairment (for example, minimal change nephropathy, acute and chronic interstitial nephritis, renal failure):* Assess renal function at beginning of treatment and periodically during treatment (5.1)
- *Mesalamine-induced Acute Intolerance Syndrome:* Has been reported. Observe patients closely for worsening of these symptoms while on treatment (5.2)
- *Hypersensitivity Reactions:* Use caution when treating patients who are hypersensitive to sulfasalazine. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported (5.3)
- *Hepatic Failure:* Has been reported in patients with pre-existing liver disease. Use caution when treating patients with liver disease (5.4)
- *Prolonged Gastric Retention in Patients with Upper Gastrointestinal Obstruction:* May lead to a delay in onset of action (5.5)

-----ADVERSE REACTIONS-----

The most common adverse reactions (observed in greater than or equal to 5 percent of adults in controlled clinical studies) were abdominal pain, eructation, pain, back pain, rash, dyspepsia, rhinitis, flu syndrome, asthenia, flatulence, vomiting, fever, arthralgia, constipation, and gastrointestinal bleeding (6.1)

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:* Renal reactions have been reported (7.1)
- *Azathioprine or 6-mercaptopurine:* Blood disorders have been reported (7.2)

-----USE IN SPECIFIC POPULATIONS-----

- *Renal Impairment:* Use Asacol with caution in patients with a history of renal disease (5.1, 7.1, 8.6)
- *Pregnancy:* May cause fetal harm, based on animal data for dibutyl phthalate (inactive ingredient in Asacol enteric coating) (8.1)
- *Nursing Mothers:* Prescribers should carefully evaluate the risks and benefits when Asacol is administered to a nursing mother (8.3)
- *Geriatric Patients:* Monitor blood cell counts in geriatric patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Mildly to Moderately Active Ulcerative Colitis

Asacol[®] (mesalamine) delayed-release tablets are 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 Ulcerative Colitis in Adults

Asacol (mesalamine) delayed-release tablets are indicated for the maintenance of remission of ulcerative colitis in adults. The safety and effectiveness of Asacol for the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Treatment of Mildly to Moderately Active Ulcerative Colitis

Adults

For adults, the recommended dosage of Asacol is two 400 mg tablets to be taken three times daily with or without food (total daily dose of 2.4 grams), for a duration of 6 weeks [see *Clinical Studies* ([14.1](#))].

Pediatrics

For pediatric patients, the recommended total daily dose of Asacol is weight-based (up to maximum of 2.4 grams/day) (see [Table 1](#)). Asacol tablets are to be taken twice daily with or without food for a duration of 6 weeks [see *Clinical Studies* ([14.1](#))].

Table 1. Pediatric Dosage by Weight

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

2.2 Dosage for Maintenance of Remission of Ulcerative Colitis in Adults

For adults, the recommended dosage of Asacol is 1.6 grams daily, in divided doses, with or without food [see *Clinical Studies* ([14.2](#))].

2.3 Important Administration Instructions

Swallow Asacol tablets whole. Do not cut, break or chew the tablets.

Two Asacol 400 mg tablets have not been shown to be bioequivalent to one Asacol[®] HD (mesalamine) delayed-release 800 mg tablet and should not be used interchangeably.

2.4 Testing Prior to Asacol Administration

Evaluate renal function prior to initiation of Asacol [see *Warnings and Precautions* (5.1)].

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 hypersensitivity to salicylates or aminosaliculates 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.

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

Prescribers should carefully evaluate the risks and benefits when using Asacol in patients with known renal impairment or history of renal disease [see *Drug Interactions* (7.1) 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 percent of controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Observe patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with Asacol.

5.3 Hypersensitivity Reactions

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Asacol or to other compounds that contain or are converted to mesalamine.

Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with Asacol and other mesalamine medications. Caution should be taken in prescribing this medicine to patients with conditions predisposing them to the development of myocarditis or pericarditis.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering Asacol to patients with liver disease.

5.5 Prolonged Gastric Retention in Patients with Upper Gastrointestinal Obstruction

Organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of Asacol which would delay release of mesalamine in the colon.

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, including renal failure [see *Warnings and Precautions (5.1)*]
- 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. Adverse reactions presented in the following sections may occur regardless of length of therapy and similar reactions have been reported in short- and long-term studies and in the postmarketing setting.

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 dose levels in children with mildly to moderately active ulcerative colitis. Clinical studies supporting the use of Asacol tablets in the maintenance of remission of ulcerative colitis included a 6-month, randomized, double-blind, placebo-controlled, multi-center study 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 in Adults

In two 6-week placebo-controlled clinical studies (Studies 1 and 2) involving 245 patients, 155 of whom were randomized to Asacol [see *Clinical Studies (14.1)*], 3.2 percent of the Asacol-treated patients discontinued therapy because of adverse reactions as compared to 2.2 percent of the placebo-treated patients. The average age of patients in Study 1 was 42 years and 48 percent of patients were male. The average age of patients in Study 2 was 42 years and 59 percent 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; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, nausea, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse reactions in patients treated with Asacol occurring at a frequency of at least 2 percent and at a rate greater than placebo in 6-week, double-blind, placebo-controlled trials (Studies 1 and 2) are listed in [Table 2](#) below.

Table 2. Adverse Reactions Reported in Two Pooled Six-Week, Placebo-Controlled Trials (Studies 1 and 2) Experienced by at Least 2 percent of Patients in the Asacol Group and at a Rate Greater than Placebo

Adverse Reaction	% of Patients with Adverse Reactions	
	Asacol (n = 152)	Placebo (n = 87)
Abdominal pain	18	14
Eructation	16	15
Pain	14	8
Back pain	7	5
Rash	6	3
Dyspepsia	6	1
Arthralgia	5	3
Vomiting	5	2
Constipation	5	1
Chest pain	3	2
Chills	3	2
Peripheral edema	3	2
Myalgia	3	1
Sweating	3	1
Pruritus	3	0
Acne	2	1
Malaise	2	1
Arthritis	2	0

Treatment of Mildly to Moderately Active Ulcerative Colitis in Pediatric Patients 5 to 17 Years Old

A randomized, double-blind, 6-week study of 2 dose 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 dose (1.2, 2.0, and 2.4 g/day for the respective body weight category) or a high dose (2.0, 3.6, and 4.8 g/day).

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

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

Table 3. Adverse Reactions Reported in One Six-Week Trial (Study 3) Experienced by at Least 5% of Patients in the Low Dose Group or High Dose Group

Adverse Reaction	% of Patients with Adverse Reactions	
	Low Dose (n=41)	High Dose (n=41)
Nasopharyngitis	15	12
Ulcerative Colitis	12	5
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 Dose = Asacol 1.2 – 2.4 g/day; High Dose = Asacol 2.0 – 4.8 g/day. Dosage was dependent on body weight. Adverse Reactions reported at the 1-week telephone follow-up visit are included.

Twelve percent of the patients in the low dose group and 5 percent of the patients in the high dose group had serious adverse reactions (ARs). Ulcerative colitis was reported as a serious AR in one subject in each group. Other serious ARs consisted of sinusitis, abdominal pain, decreased body mass index, adenovirus infection, bloody diarrhea, sclerosing cholangitis, and pancreatitis in one subject each in the low dose group and anemia and syncope in one subject each in the high dose group.

Seven patients were withdrawn from the study because of ARs: 5 (12 percent) in the low dose group (ulcerative colitis, adenovirus infection, sclerosing cholangitis, pancreatitis) and 2 (5 percent) in the high dose group (increased amylase and increased lipase, 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 Ulcerative Colitis in Adults

In a 6-month placebo-controlled maintenance trial involving 264 patients (Study 4) 177 of whom were randomized to Asacol, six (3.4 percent) of the patients using Asacol discontinued therapy because of adverse reactions, as compared to four (4.6 percent) of patients using placebo [*see Clinical Studies (14.2)*]. The average age of patients in Study 4 was 42 years and 55 percent of patients were male. Adverse reactions leading to study withdrawal in patients using Asacol included (each in one patient): anxiety; headache; pruritus; decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

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

In 3342 patients in uncontrolled clinical studies, the following adverse reactions occurred at a frequency of 5 percent or greater and appeared to increase in frequency with increasing dose: asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis.

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

No formal drug interaction studies have been performed using Asacol with other drugs. However, the following interactions between mesalamine-containing products and other drugs have been reported.

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 renal 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well controlled studies of Asacol use in pregnant women. Limited published human data on mesalamine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Furthermore, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4 percent for major malformations, and 15 to 20 percent for pregnancy loss. No evidence of 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. 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 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 to the fetus.

Human Data

Mesalamine crosses the placenta. In prospective and retrospective studies of over 600 women exposed to mesalamine during pregnancy, the observed rate of congenital malformations was not increased above the background rate in the general population. Some data show an increased rate of preterm birth, stillbirth, and low birth weight, but it is unclear whether this was due to underlying maternal disease, drug exposure, or both, as active inflammatory bowel disease is also associated with adverse pregnancy outcomes.

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.

Dibutyl phthalate (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.

8.3 Nursing Mothers

Mesalamine and its N-acetyl metabolite are present in human milk. 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 doses 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.

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.

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 child from the drug or from the underlying maternal condition. Exercise caution when Asacol is administered to a nursing woman.

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 pediatric patients [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)*].

Asacol was studied in a randomized, double-blind, parallel-group, 6-week treatment study of two dose levels of Asacol in 82 pediatric patients 5 to 17 years of age with mildly to moderately active ulcerative colitis. 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 dose (1.2, 2.0, and 2.4 g/day for the respective weight category) or a high dose (2.0, 3.6, and 4.8 g/day). Baseline and screening visits were followed by a treatment period of 6 weeks [*see Dosage and Administration (2.1)*]. The high dose was not more effective than the low dose and is not an approved dosage [*see Clinical Studies (14.1)*].

The safety and effectiveness of Asacol in pediatric patients below the age of 5 years have not been established. The safety and effectiveness of Asacol in the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Asacol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. 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. Reports from uncontrolled clinical studies and postmarketing reporting systems suggest a higher incidence of blood dyscrasias, that is, agranulocytosis, neutropenia, pancytopenia, in subjects receiving Asacol who are 65 years or older. Caution should be taken to closely monitor blood cell counts during treatment with Asacol.

8.6 Renal Impairment

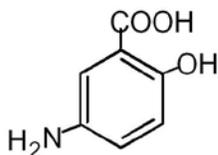
Mesalamine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol therapy and periodically while on Asacol therapy [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.1)].

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 copolymer type B, NF), 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 copolymer B (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 percent 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.

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 PK study evaluating 30, 60 and 90 mg/kg/day doses of Asacol administered twice daily for four weeks, the mean 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 dose level (that is, 1.2, 2.0 or 2.4 g/day based on body weight strata of 17 to greater than 33 kg, 33 to less than 54 kg, and 54 to less than 90 kg, respectively).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mesalamine was not carcinogenic at dietary doses 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 the maximum recommended maintenance dose of Asacol of 1.6 g/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 doses up to 480 mg/kg/day (about 1.9 times the recommended human treatment dose 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 g/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 tablets in patients with mildly to moderately active ulcerative colitis.

In one randomized, double-blind, multi-center trial of 158 patients (Study 1), Asacol doses of 1.6 g/day and 2.4 g/day for 6 weeks were compared to placebo. 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 dose of 2.4 g/day, 21 of 43 (49 percent) patients using Asacol tablets showed an improvement in sigmoidoscopic appearance of the bowel compared to 12 of 44 (27 percent) patients using placebo ($p = 0.048$). In addition, significantly more patients in the Asacol tablets 2.4 g/day group showed improvement in rectal bleeding and stool frequency. The 1.6 g/day dose did not produce consistent evidence of effectiveness.

In a second randomized, double-blind, placebo-controlled clinical trial of 6 weeks duration in 87 patients (Study 2), Asacol tablets, at a dose of 4.8 g/day, for 6 weeks, resulted in sigmoidoscopic improvement in 28 of 38 (74 percent) patients compared to 10 of 38 (26 percent) placebo patients (p less than 0.001). Also, more patients in the Asacol tablets 4.8 g/day group than the placebo group showed improvement in overall symptoms.

The 4.8 g/day dose is not an approved dosage for the treatment of mildly to moderately active ulcerative colitis.

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 2 dose levels of Asacol (Study 3) was conducted in 82 pediatric patients 5 to 17 years of age with mildly or moderately active ulcerative colitis. 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 dose (1.2, 2.0, and 2.4 g/day for the respective weight category) or a high dose (2.0, 3.6, and 4.8 g/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 subscores of the Mayo Score) and based on the Pediatric Ulcerative Colitis Activity Index (PUCAI) (which included assessment of abdominal pain, rectal bleeding, stool consistency and frequency, presence of nocturnal bowel movement and level of activity) 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 dose group and 41 patients in the high dose group who received at least one dose of Asacol; 36 patients in each dose 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, 73.2 percent of the patients in the low dose group, and 70.0 percent of the patients in the high dose group achieved success based on the TM-Mayo; 34.1 percent of the patients in the low dose group and 42.5 percent of the patients in the high dose group achieved complete response. At Week 6, 56.1 percent of the patients in the low dose group, and 55.0 percent of the patients in the high dose group achieved success based on the PUCAI; 46.3 percent of the patients in the low dose group and 42.5 percent of the patients in the high dose group achieved complete response.

The high dose was not more effective than the low dose and is not an approved dosage [*see Dosage and Administration (2.1)*].

14.2 Maintenance of Remission of Ulcerative Colitis in Adults

A 6-month, randomized, double-blind, placebo-controlled, multi-center study (Study 4) involved 264 patients treated with Asacol tablets 0.8 g/day (n = 90), 1.6 g/day (n = 87), or placebo (n = 87). In the 0.8 g/day arm, patients were dosed twice daily; in the 1.6 g/day arm, patients were dosed four times daily. The proportion of patients treated with 0.8 g/day who maintained endoscopic remission was not statistically significant compared to placebo. The proportion of patients using Asacol tablets 1.6 g/day who maintained endoscopic remission of ulcerative colitis was in 61 of 87 (70.1 percent) compared with 42 of 87 (48.3 percent) of placebo patients (p = 0.005).

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Asacol (mesalamine) Delayed-Release Tablets are available as 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

- 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 if they are switching from a previous oral mesalamine therapy to Asacol they should discontinue their previous oral mesalamine therapy and follow the dosing instructions for Asacol. Inform patients that they should not substitute two Asacol 400 mg tablets with one Asacol HD 800 mg tablet [see *Dosage and Administration* (2.3)].
- 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.
- 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.

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