Sponsor Final Labeling Dated 28 MAY 08

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[TRADENAME] (mesalamine) delayed-release tablet for oral administration

Initial U.S. Approval: 1987

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

- [TRADENAME] is a locally acting aminosalicylate indicated for the treatment of moderately active ulcerative colitis (1)

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

- Two 800 mg tablets three times daily for 6 weeks (2)
- [TRADENAME] should be swallowed whole without cutting, breaking, or chewing (2)

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

- 800 mg delayed-release tablet (3)

----------CONTRAINDICATIONS----------

- History of hypersensitivity to salicylates or aminosalicylates or to any component of the [TRADENAME] tablet (4)

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

- Renal impairment may occur. Monitor renal function at the beginning of treatment and periodically during therapy (5.1)
- Acute exacerbation of colitis symptoms can occur (5.2)
- Patients with pyloric stenosis may have prolonged gastric retention of [TRADENAME] tablets (5.4)

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

- The most common adverse reactions (observed in >2% of patients) were headache, nausea, nasopharyngitis, abdominal pain, and worsening of ulcerative colitis (6.1)
- **To report SUSPECTED ADVERSE REACTIONS, contact Procter & Gamble Pharmaceuticals at 800-836-0658 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***

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

- Use with caution in patients with renal disease (5.1)
- Monitor blood cell counts in geriatric patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised 5/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Sponsor Final Labeling Dated 28 MAY 08

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

[TRADENAME] is indicated for the treatment of moderately active ulcerative colitis. Safety and effectiveness of [TRADENAME] beyond 6 weeks has not been established.

2 DOSAGE AND ADMINISTRATION

For the treatment of moderately active ulcerative colitis, the recommended dose of [TRADENAME] in adults is two 800 mg tablets to be taken three times daily with or without food, for a total daily dose of 4.8 g, for a duration of 6 weeks. [TRADENAME] use beyond 6 weeks has not been evaluated. [TRADENAME] should be swallowed whole without cutting, breaking, or chewing.

3 DOSAGE FORMS AND STRENGTHS

[TRADENAME] delayed-release tablets are available as red-brown, capsule-shaped tablets containing 800 mg mesalamine and imprinted with “PG 800” in black.

4 CONTRAINDICATIONS

[TRADENAME] is contraindicated in patients with hypersensitivity to salicylates or aminosalicylates or to any of the components of [TRADENAME] tablets.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients taking products such as [TRADENAME] that contain or are converted to mesalamine.

It is recommended that all patients have an evaluation of renal function prior to initiation of [TRADENAME] and periodically while on therapy. Exercise caution when using [TRADENAME] in patients with known renal dysfunction or history of renal disease.

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity *[see Nonclinical Toxicology (13.2)]*.

5.2 Exacerbation of Ulcerative Colitis Symptoms

Exacerbation of the symptoms of colitis has been reported in 2.3% of [TRADENAME]-treated patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of [TRADENAME] tablets as well as other mesalamine products. Symptoms usually abate when [TRADENAME] tablets are discontinued.

5.3 Hypersensitivity

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

5.4 Pyloric Stenosis

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

6 ADVERSE REACTIONS

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

- Renal impairment, including renal failure (rare) *[see Warnings and Precautions (5.1)]*
- Acute exacerbation of colitis *[see Warnings and Precautions (5.2)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.3)]*

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.

[TRADENAME] has been evaluated in 896 patients with ulcerative colitis in controlled studies. Three six-week, active-controlled studies were conducted comparing [TRADENAME] 4.8 g/day with Asacol (mesalamine) 2.4 g/day as control in patients with mildly to moderately active ulcerative colitis. In these studies, 727 patients were dosed with the [TRADENAME] tablet and 732 patients were dosed with the Asacol 400 mg tablet. (One [TRADENAME] 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets *[see Clinical Pharmacology (12.3)]*.)

The most common reactions reported in the [TRADENAME] group were headache (4.7%), nausea (2.8%), nasopharyngitis (2.5%), abdominal pain (2.3%), exacerbation of ulcerative colitis (2.3%), diarrhea (1.7%), and dyspepsia (1.7%); Table 1 enumerates adverse drug reactions that occurred in the three studies. The most common reactions in the primary efficacy population of patients with moderately active ulcerative colitis (602 patients dosed with [TRADENAME] and 618 patients dosed with the Asacol 400 mg tablet) were the same as all treated patients. The majority of adverse reactions with [TRADENAME] in the double-blind, active-controlled trials were mild or moderate in severity and were reversible.

Discontinuations due to adverse reactions occurred in 3.9% of patients in the [TRADENAME] group and in 4.2% of patients in the Asacol 400 mg tablet comparator group. The most common cause for discontinuation was gastrointestinal symptoms associated with ulcerative colitis.

Severe adverse reactions occurred in 7.6% of patients in the [TRADENAME] group and in 7.6% of patients in the Asacol 400 mg tablet comparator group. Most of these reactions were gastrointestinal symptoms related to ulcerative colitis. Serious adverse reactions occurred in 0.8% of patients in the [TRADENAME] group and in 1.8% of patients in the Asacol 400 mg tablet comparator group. The majority involved the gastrointestinal system.

Table 1. Adverse Reactions Occurring in 1% or More of All Treated Patients (Three studies combined; Intent-to-treat population)

MedDRA Preferred Term	Asacol* 2.4g/day (400 mg Tablet) (N=732)	[TRADENAME]* 4.8g/day (800 mg Tablet) (N=727)
Headache	4.9 %	4.7 %
Nausea	2.9 %	2.8 %
Nasopharyngitis	1.4 %	2.5 %
Abdominal pain	2.3 %	2.3 %
Ulcerative Colitis	2.7 %	2.3 %
Diarrhea	1.9 %	1.7 %
Dyspepsia	0.8 %	1.7 %
Vomiting	1.6 %	1.4 %
Flatulence	0.7 %	1.2 %
Influenza	1.2 %	1.0 %
Pyrexia	1.2 %	0.7 %
Cough	1.4 %	0.3 %

N = number of patients within specified treatment group
% =percentage of patients in category and treatment group
*One [TRADENAME] 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets *[see Clinical Pharmacology (12.3)]*.

6.2 Adverse Reaction Information from Other Sources

In addition to the adverse reactions reported above in clinical trials involving the [TRADENAME] tablet, the adverse events listed below have been reported in controlled clinical trials, open label studies, literature reports, or foreign and domestic marketing experience with Asacol 400 mg tablets or other products that contain or are metabolized to mesalamine. 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: Facial edema, edema, peripheral edema, asthenia, chills, infection, malaise, pain, neck pain, chest pain, back pain, abdominal enlargement, lupus-like syndrome, drug fever (rare).

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

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

Hepatic: There have been rare reports of hepatotoxicity, including jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome, that included changes in liver enzymes, was also reported.

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

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

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

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

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

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

Renal/Urogenital: Renal failure (rare), interstitial nephritis, minimal change nephropathy [*see Warnings and Precautions (5.1)*], dysuria, urinary frequency and urgency, hematuria, epididymitis, decreased libido, dysmenorrhea, menorrhagia.

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 [TRADENAME] with other drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: Reproduction studies have been performed in rats at oral doses up to 480 mg/kg/day (about 0.8 times the recommended human treatment dose of 4.8 g/day based on body surface area) and rabbits at oral doses up to 480 mg/kg/day (about 1.6 times the recommended human treatment dose of 4.8 g/day based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Mesalamine is known to cross the placental barrier.

8.3 Nursing Mothers

Mesalamine and its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined. Caution should be exercised when [TRADENAME] is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of [TRADENAME] in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of [TRADENAME] 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 [TRADENAME]. Reports from uncontrolled clinical studies and postmarketing reporting systems for Asacol (mesalamine) suggested a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in patients who

were 65 years or older. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

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 [TRADENAME] therapy and periodically while on [TRADENAME] therapy *[see Warnings and Precautions (5.1)]*.

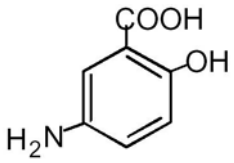
10 OVERDOSAGE

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

Single oral doses of 5000 mg/kg mesalamine suspension in mice (approximately 4.2 times the recommended human dose of [TRADENAME] based on body surface area), 4595 mg/kg in rats (approximately 7.8 times the recommended human dose of [TRADENAME] based on body surface area) and 3000 mg/kg in cynomolgus monkeys (approximately 10 times the recommended human dose of [TRADENAME] based on body surface area) were lethal.

11 DESCRIPTION

Each [TRADENAME] delayed-release tablet for oral administration contains 800 mg of mesalamine, an anti-inflammatory drug. [TRADENAME] delayed-release tablets have an outer protective coat consisting of a combination of acrylic based resins, Eudragit S (methacrylic acid copolymer B, NF) and Eudragit L (methacrylic acid copolymer A, NF). The inner coat consists of an acrylic based resin, Eudragit S, which dissolves at pH 7 or greater, releasing 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: $C_7H_7NO_3$

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), methacrylic acid copolymer A (Eudragit L), 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 (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

12.3 Pharmacokinetics

Plasma concentrations of mesalamine (5-aminosalicylic acid; 5-ASA) and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA) are highly variable following administration of [TRADENAME] tablets. The time to peak plasma concentration (t_{max}) is prolonged for mesalamine and N-Ac-5-ASA with the median values from various studies ranging from 10 to 16 hours, reflecting the delayed-release characteristics. Based on cumulative urinary recovery of mesalamine and N-Ac-5-ASA from single dose studies in healthy volunteers, approximately 20% of the orally administered mesalamine in [TRADENAME] tablets is systemically absorbed. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver to N-Ac-5-ASA which is excreted mainly by the kidney. The PK parameters following administration of 1600 mg three times daily in healthy subjects are shown in Table 2.

Table 2. Mean (± S.D.) PK parameters in healthy subjects following administration of two 800 mg tablets three times daily for 6 days (n=16)

	Mesalamine	N-Ac-5-ASA
AUC_{tau} (mcg h/mL)	20 ± 14	25 ± 11
C_{max} (mcg/mL)	5.0 ± 4.0	4.6 ± 2.5
$t_{1/2}$ (h)	12.6 ± 10.9[*]	23.6 ± 11.2[#]

[*] n=11, [#]n=6

A high fat meal does not affect the extent of systemic exposure to mesalamine after single-dose administration of [TRADENAME], but mesalamine C_{max} decreases by 47% and t_{max} is delayed by 14 hours under fed conditions.

One [TRADENAME] 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets. In a single dose, cross-over pharmacokinetic study in 20 healthy volunteers, the mean mesalamine C_{max} was 36% lower and the mean mesalamine AUC was 25% lower with administration of one [TRADENAME] 800 mg tablet relative to two Asacol 400 mg tablets. Because the mechanism of action of mesalamine appears to be topical, the impact of these differences in measures of systemic exposure on clinical efficacy is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are approximately 0.8 and 1.7 times the 4.8 g/day [TRADENAME] dose (based on body surface area). Mesalamine was not genotoxic in the Ames test, the Chinese hamster ovary cell chromosomal aberration assay, and the mouse micronucleus test. Mesalamine, at oral doses up to 480

mg/kg/day (about 0.8 times the recommended human treatment dose based on body surface area), 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 4.8 g/day dose for a 50 kg person.)

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (1.3 to 1.7 times the recommended human dose). Doses of 170 and 360 mg/kg/day (about 0.3 and 0.6 times the recommended human dose) 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 (approximately 3.4 times the recommended human dose) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 6.25 times the recommended human dose) 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 (0.5 times the recommended human dose).

14 CLINICAL STUDIES

14.1 Moderately Active Ulcerative Colitis

The efficacy of [TRADENAME] at 4.8 g/day was studied in a six-week, randomized, double-blind, active-controlled study in 772 patients with moderately active ulcerative colitis (UC). Moderately active UC was defined as a Physician's Global Assessment (PGA) score of 2; the PGA is a four-point scale (0-3) that encompasses the clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy findings.

Patients were randomized 1:1 to the [TRADENAME] 4.8 g/day group (two [TRADENAME] tablets three times a day) or the Asacol (mesalamine) 2.4 g/day group (two Asacol 400 mg tablets three times a day). (One [TRADENAME] 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets *[see Clinical Pharmacology (12.3)]*.)

Patients characteristically had a history of previous use of oral 5-ASAs (86%), steroids (41%), and rectal therapies (49%), and demonstrated clinical symptoms of three or more stools over normal per day (87%) and obvious blood in the stool most or all of the time (70%). The study population was primarily Caucasian (97%), had a mean age of 43 years (8% aged 65 years or older), and included slightly more males (56%) than females (44%).

The primary endpoint was treatment success defined as improvement from baseline to Week 6 based on the PGA. Treatment success rates were similar in the two groups: 70% in the [TRADENAME] group and 66% in the Asacol group (difference: 5%; 95% CI: [-1.9%, 11.2%]).

A second controlled study supported the efficacy of [TRADENAME] at 4.8 g/day. Treatment success was 72% in patients with moderately active UC treated with [TRADENAME].

Sponsor Final Labeling Dated 28 MAY 08

16 HOW SUPPLIED/STORAGE AND HANDLING

[TRADENAME] tablets are available as red-brown, capsule-shaped tablets containing 800 mg mesalamine and imprinted with “PG 800” in black.

NDC 0149-0783-01 Bottle of 180

Store at controlled room temperature 20° to 25°C (68° to 77°F) [See USP].

17 PATIENT COUNSELING INFORMATION

- Instruct patients to swallow the [TRADENAME] tablets whole, taking care not to break, cut, or chew the tablets, because the outer coating is an important part of the delayed-release formulation.

- Inform patients that if they are switching from a previous oral mesalamine therapy to [TRADENAME] they should discontinue their previous oral mesalamine therapy and follow the dosing instructions for [TRADENAME]. Inform patients that they should not substitute one [TRADENAME] tablet with two Asacol 400 mg tablets *[see Dosage Forms and Strengths (3) and Clinical Pharmacology (12.3)]*.

- 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 [TRADENAME] tablets from moisture. Instruct patients to close the container tightly and to leave any desiccant pouches present in the bottle along with the tablets.

Procter & Gamble Pharmaceuticals
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under license from Medeva Pharma Suisse AG
[registered trademark owner.]
Made in Germany, D-64331 Weiterstadt

U.S. Patent Nos. 5,541,170; 5,541,171; and 6,893,662 and other patents pending.