

MESALAMINE- mesalamine tablet, delayed release
Zydus Pharmaceuticals (USA) Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MESALAMINE DELAYED-RELEASE TABLETS safely and effectively. See full prescribing information for MESALAMINE DELAYED-RELEASE TABLETS.

Mesalamine delayed-release tablets, for oral use

Initial U.S. Approval: 1987

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

Mesalamine delayed-release tablets is an aminosalicylate indicated for the treatment of moderately active ulcerative colitis in adults. (1)

Limitation of Use: Safety and effectiveness of Mesalamine delayed-release tablets beyond 6 weeks have not been established (1)

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

- Recommended dosage is two 800 mg tablets three times daily (4.8 grams/day) with or without food for 6 weeks (2.1)
- Instruct patients to swallow tablets whole without cutting, breaking, or chewing (2.2)
- One Mesalamine delayed-release 800 mg tablet cannot be substituted for two Asacol® (mesalamine) delayed-release 400 mg tablets (2.2)
- Recommend that renal function be evaluated prior to initiation of Mesalamine delayed-release tablets (2.3, 5.1)

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

Delayed-release tablets: 800 mg (3)

----- **CONTRAINDICATIONS** -----

- Patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Mesalamine delayed-release 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 therapy (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 2 percent of patients) were headache, nausea, nasopharyngitis, abdominal pain, and worsening of ulcerative colitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 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 Mesalamine delayed-release tablets 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 Mesalamine delayed-release tablets enteric coating) (8.1)
- *Nursing Mothers:* Prescribers should carefully evaluate the risks and benefits when Mesalamine delayed-release tablets are administered to a nursing mother. (8.3)
- *Geriatric Patients:* Monitor blood cell counts in geriatric patients (8.5)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

2.2 Important Administration Instructions

2.3 Testing Prior to Mesalamine delayed-release tablets Administration

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

5.5 Prolonged Gastric Retention in Patients with Upper Gastrointestinal Obstruction

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

8.3 Nursing Mothers

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 Moderately Active Ulcerative Colitis

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

Mesalamine delayed-release tablets are indicated for the treatment of moderately active ulcerative colitis in adults. Safety and effectiveness of Mesalamine delayed-release tablets beyond 6 weeks have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

For the treatment of moderately active ulcerative colitis, the recommended dosage of Mesalamine delayed-release tablets 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 grams, for a duration of 6 weeks.

2.2 Important Administration Instructions

Swallow Mesalamine delayed-release tablets whole, do not cut, break or chew the tablets.

One Mesalamine delayed-release 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets [see *Clinical Pharmacology (12.3)*].

2.3 Testing Prior to Mesalamine delayed-release tablets Administration

It is recommended that all patients have an evaluation of renal function prior to initiation of Mesalamine delayed-release tablets [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

Mesalamine delayed-release tablets: 800 mg (red-brown, capsule-shaped and imprinted with "WC 800" in black).

4 CONTRAINDICATIONS

Mesalamine delayed-release tablets are contraindicated in patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Mesalamine delayed-release tablets [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, rarely, renal failure, has been reported in patients taking products such as delayed-release tablets that contain or are converted to mesalamine.

It is recommended that all patients have an evaluation of renal function prior to initiation of Mesalamine delayed-release tablets and periodically while on therapy. Prescribers should carefully evaluate the risks and benefits when using Mesalamine delayed-release tablets 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. Exacerbation of the symptoms of colitis has been reported in 2.3 percent of Mesalamine delayed-release tablets-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 Mesalamine delayed-release tablets as well as other mesalamine products. Symptoms usually abate when

Mesalamine delayed-release tablets are discontinued.

5.3 Hypersensitivity Reactions

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Mesalamine delayed-release tablets or to other compounds that contain or are converted to mesalamine.

Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with Mesalamine delayed-release tablets 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 Mesalamine delayed-release tablets 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 Mesalamine delayed-release tablets which would delay release of mesalamine in the colon.

6 ADVERSE REACTIONS

The most serious adverse reactions seen in Mesalamine delayed-release tablets clinical trials or with other products that contain mesalamine or are metabolized to mesalamine were:

- Renal impairment, including renal failure (rare) [*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.

Mesalamine delayed-release tablets have been evaluated in 896 patients with ulcerative colitis in controlled studies. Three six-week, active-controlled studies were conducted comparing Mesalamine delayed-release tablets 4.8 grams/day with Asacol (mesalamine) 2.4 grams/day in patients with mildly to moderately active ulcerative colitis. In these studies, 727 patients were dosed with the Mesalamine delayed-release tablet and 732 patients were dosed with the Asacol 400 mg tablet. (One Mesalamine delayed-release 800 mg tablet cannot be substituted for two Asacol 400 mg tablets [*see Clinical Pharmacology (12.3)*].)

The most common reactions reported in the Mesalamine delayed-release tablets group were headache (4.7 percent), nausea (2.8 percent), nasopharyngitis (2.5 percent), abdominal pain (2.3 percent), exacerbation of ulcerative colitis (2.3 percent), diarrhea (1.7 percent), and dyspepsia (1.7 percent); Table 1 enumerates adverse reactions that occurred in the three studies. The most common reactions in patients with moderately active ulcerative colitis (602 patients dosed with Mesalamine delayed-release tablets and 618 patients dosed with the Asacol 400 mg) were the same as all treated patients.

Discontinuations due to adverse reactions occurred in 3.9 percent of patients in the Mesalamine delayed-release tablets group and in 4.2 percent 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 percent of patients in the Mesalamine delayed-release tablets group and in 7.6 percent 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 percent of patients in the Mesalamine delayed-release tablets group and in 1.8 percent of patients in the Asacol 400 mg tablet comparator group. The majority involved the gastrointestinal system.

Table 1. Adverse Reactions Occurring in 1 Percent or More of All Treated Patients (Three studies combined)

Adverse Reaction	Asacol*2.4 g/day(400 mg Tablet)(N = 732)	Mesalamine delayed-release tablets * 4.8 g/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

Percent = percentage of patients in category and treatment group

*One Mesalamine delayed-release 800 mg tablet cannot be substituted for two Asacol 400 mg tablets [see *Clinical Pharmacology (12.3)*].

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving the Mesalamine delayed-release 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 mesalamine 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) and myocarditis (rare) [see *Warnings and Precautions (5.3)*], pericardial effusion, 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 [*see Warnings and Precautions (5.4)*].

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 Mesalamine delayed-release tablets 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 well controlled studies of Mesalamine delayed-release tablets 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 1.6 times (rat) and 3.2 times (rabbit) the recommended human dose. However, dibutyl phthalate (DBP) is an inactive ingredient in Mesalamine delayed-release tablets' enteric coating, and in

animal studies in rats at doses higher than 80 times the human dose, maternal DBP was associated with external and skeletal malformations and adverse effects on the male reproductive system. Mesalamine delayed-release tablets 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 1.6 times (rat) and 3.2 times (rabbit) the recommended human dose, based on body surface area.

Dibutyl phthalate (DBP) is an inactive ingredient in Mesalamine delayed-release tablets' enteric coating. The human daily intake of DBP from the maximum recommended dose of Mesalamine delayed-release tablets is about 48 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 17 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 84 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 106 times the human dose, based on body surface area) and skeletal abnormalities (greater than or equal to 750 mg/kg/day, about 127 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 Mesalamine delayed-release 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 Mesalamine delayed-release tablets and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Exercise caution when Mesalamine delayed-release tablets are administered to a nursing mother.

8.4 Pediatric Use

Safety and effectiveness of Mesalamine delayed-release tablets in pediatric patients have not been established. See the prescribing information for other approved mesalamine products for the safety and

effectiveness of these products in pediatric patients.

8.5 Geriatric Use

Clinical studies of Mesalamine delayed-release tablets 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 Mesalamine delayed-release tablets. Reports from uncontrolled clinical studies and postmarketing reporting systems for Asacol (mesalamine) suggested a higher incidence of blood dyscrasias, that is, agranulocytosis, neutropenia, pancytopenia, in patients who were 65 years or older. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

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 Mesalamine delayed-release tablets therapy and periodically while on Mesalamine delayed-release tablets therapy [*see Dosage and Administration (2.3), Warnings and Precautions (5.1)*].

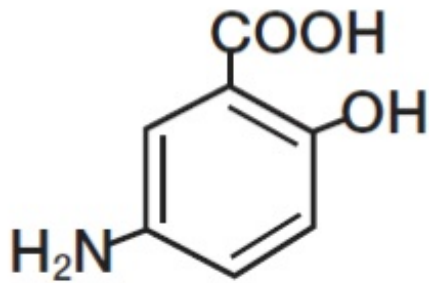
10 OVERDOSAGE

There is no specific antidote for mesalamine overdose and treatment for suspected acute severe toxicity with Mesalamine delayed-release tablets 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. Mesalamine delayed-release tablets are 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 Mesalamine delayed-release tablets based on body surface area), 4595 mg/kg in rats (approximately 7.8 times the recommended human dose of Mesalamine delayed-release tablets based on body surface area) and 3000 mg/kg in cynomolgus monkeys (approximately 10 times the recommended human dose of Mesalamine delayed-release tablets based on body surface area) were lethal.

11 DESCRIPTION

Each Mesalamine delayed-release tablet for oral administration contains 800 mg of mesalamine, an aminosalicylate. Mesalamine 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: 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), 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, that is, prostanoids, and through the lipoxygenase pathways, that is, 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 Mesalamine delayed-release 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 percent of the orally administered mesalamine in Mesalamine delayed-release 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 (\pm 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 \pm 14	25 \pm 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 Mesalamine delayed-release tablets, but mesalamine C_{max} decreases by 47 percent and t_{max} is delayed by 14 hours under fed conditions.

One Mesalamine delayed-release 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 percent lower and the mean mesalamine AUC was 25 percent lower with administration of one Mesalamine delayed-release 800 mg tablets 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 Mesalamine delayed-release tablets 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 Mesalamine delayed-release tablets 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 to 3) that encompasses the clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy findings.

Patients were randomized 1:1 to the Mesalamine delayed-release tablets 4.8 g/day group (two Mesalamine delayed-release tablets three times a day) or the Asacol (mesalamine) 2.4 g/day group (two Asacol 400 mg tablets three times a day). (One Mesalamine delayed-release 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 percent), steroids (41 percent), and rectal therapies (49 percent), and demonstrated clinical symptoms of three or more stools over normal per day (87 percent) and obvious blood in the stool most or all of the time (70 percent). The study population was primarily Caucasian (97 percent), had a mean age of 43 years (8 percent aged 65 years or older), and included slightly more males (56 percent) than females (44 percent).

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 percent in the Mesalamine delayed-release tablets group and 66 percent in the Asacol group (difference: 5 percent; 95 percent CI: [-1.9 percent, 11.2 percent]).

A second controlled study supported the efficacy of Mesalamine delayed-release tablets at 4.8 g/day. Treatment success was 72 percent in patients with moderately active UC treated with Mesalamine delayed-release tablets.

16 HOW SUPPLIED/STORAGE AND HANDLING

Mesalamine delayed-release tablets are available as red-brown, capsule-shaped tablets containing 800 mg mesalamine and imprinted with "WC 800" in black.

NDC 68382-484-28 Bottle of 180 tablets

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

17 PATIENT COUNSELING INFORMATION

- Instruct patients to swallow the Mesalamine delayed-release 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 Mesalamine delayed-release tablets they should discontinue their previous oral mesalamine therapy and follow the dosing instructions for Mesalamine delayed-release tablets. Inform patients that they should not substitute one Mesalamine delayed-release tablet with two Asacol 400 mg tablets [see *Dosage and Administration (2.2)* 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 Mesalamine delayed-release 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 Mesalamine delayed-release tablets contain dibutyl phthalate, which caused malformations and adverse effects on the male reproductive system in animal studies. Dibutyl phthalate is excreted in human milk.

Distributed By:

Zydus Pharmaceuticals USA Inc.

Pennington, NJ 08534

Asacol® is a registered trademark of Medeva Pharma Suisse AG, licensed to Allergan Pharmaceuticals International Limited. © 2016 Allergan. All rights reserved.

Rev. 03/2016

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Principal Display Panel

NDC 68382-484-28

Mesalamine Delayed-release Tablets

800 mg per tablet

180 Tablets

Rx Only

The image shows the principal display panel for Mesalamine Delayed-Release Tablets. It features the ZyGenerics logo at the top left, followed by the NDC number 68382-484-28. The product name 'MESALAMINE DELAYED-RELEASE Tablets' is prominently displayed in blue. Below this, the strength '800 mg' and 'Rx Only' are shown in a green box. The quantity '180 Tablets' is at the bottom left. On the right side, there is a barcode with the NDC number 68382-484-28 printed vertically. Text on the right includes: 'Each delayed-release tablet contains 800 mg of Mesalamine.', 'Store at controlled room temperature 20° – 25°C (68° – 77°F) [See USP].', 'For the treatment of moderately active ulcerative colitis, the recommended dose of Mesalamine delayed-release tablets 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.', 'See package outsert for Full Prescribing Information.', 'Do not break, crush, or chew the tablet. Swallow whole with water.', 'Distributed by: Zydus Pharmaceuticals USA Inc. Pennington, NJ 08534'. A QR code and lot number '116791' are also present. A hatched area at the bottom right is labeled 'Lot: Exp.'. The number '55489US10' is at the bottom right corner.

MESALAMINE

mesalamine tablet, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68382-484
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MESALAMINE (UNII: 4Q81I59GXC) (MESALAMINE - UNII:4Q81I59GXC)	MESALAMINE	800 mg

Inactive Ingredients

Ingredient Name	Strength
DIBUTYL PHTHALATE (UNII: 2286E5R2KE)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:2) (UNII: 5KY68S2577)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONE (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	BROWN (red-brown)	Score	no score
Shape	CAPSULE (capsule-shaped)	Size	19 mm
Flavor		Imprint Code	WC;800
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68382-484-28	180 in 1 BOTTLE; Type 0: Not a Combination Product	08/01/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021830	08/01/2016	

Labeler - Zydus Pharmaceuticals (USA) Inc. (156861945)

Establishment

Name	Address	ID/FEI	Business Operations
Warner Chilcott Deutschland GmbH		315592121	ANALYSIS(68382-484) , MANUFACTURE(68382-484)

Revised: 8/2017

Zydus Pharmaceuticals (USA) Inc.