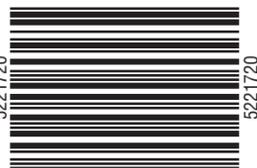


MESALAMINE
EXTENDED-RELEASE
CAPSULES, USP
500 mg
Rx only



MESALAMINE EXTENDED-RELEASE CAPSULES, USP

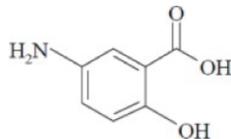
500 mg
Rx only

DESCRIPTION

Mesalamine extended-release capsules, USP for oral administration are extended-release formulation of mesalamine, USP, an aminosaliclylate anti-inflammatory agent for gastrointestinal use.

Chemically, mesalamine, USP is benzoic acid, 5-amino-2-hydroxy. It has a molecular weight of 153.14.

The structural formula is:



Each 500 mg mesalamine extended-release capsule contains 500 mg of mesalamine, USP. It also contains the following inactive ingredients: castor oil, colloidal silicon dioxide, diacetylated monoglyceride, ethylcellulose, hypromellose, stearic acid, sugar spheres (corn starch and sucrose), talc, and white wax. The capsule shell contains FD&C Blue 1, gelatin, sodium lauryl sulfate, and titanium dioxide. The imprinting ink contains ferrosulfate, potassium hydroxide, and shellac. FDA approved dissolution test specifications differ from USP.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2 to 4 g per day in divided doses. Four grams of sulfasalazine provide 1.6 g of free mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is not fully understood, but it appears to be a topical anti-inflammatory effect on colonic epithelial cells. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways (i.e., prostanooids) and through the lipoxygenase pathways (i.e., leukotrienes (LTs)) and hydroxyicosatetraenoic acids (HETEs), is increased in patients with ulcerative colitis, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Human Pharmacokinetics and Metabolism

Absorption: Mesalamine extended-release capsules are ethylcellulose-coated, extended-release formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. Based on urinary excretion data, 20% to 30% of the mesalamine in mesalamine extended-release capsules is absorbed. In contrast, when mesalamine is administered orally as an unformulated 1-g aqueous suspension, mesalamine is approximately 80% absorbed. Plasma mesalamine concentration peaked at approximately 1 mcg/mL 3 hours following a 1-g mesalamine dose and declined in a biphasic manner. The literature describes a mean terminal half-life of 42 minutes for mesalamine following intravenous administration.

Because of the continuous release and absorption of mesalamine from mesalamine extended-release capsule throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration. N-acetyl-5-aminosalicylic acid, the major metabolite of mesalamine (5-aminosalicylic acid), peaked at approximately 3 hours at 1.8 mcg/mL, and its concentration followed a biphasic decline. Pharmacological activities of N-acetyl-5-aminosalicylic acid are unknown, and other metabolites have not been identified.

Oral mesalamine pharmacokinetics were nonlinear when mesalamine extended-release capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalamine plasma concentrations increasing about nine times, from 0.14 mcg/mL to 1.21 mcg/mL, suggesting saturable first-pass metabolism. N-acetyl-5-aminosalicylic acid pharmacokinetics were linear.

Elimination: About 130 mg free mesalamine was recovered in the feces following a single 1-g mesalamine dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with mesalamine dose. N-acetyl-5-aminosalicylic acid was the primary compound excreted in the urine (19% to 30%) following mesalamine dosing.

CLINICAL TRIALS

In two randomized, double-blind, placebo-controlled, dose-response trials (UC-1 and UC-2) of 625 patients with active mild to moderate ulcerative colitis, mesalamine, at an oral dose of 4 g/day given 1 g four times daily, produced consistent improvement in prospectively identified primary efficacy parameters, PGA, Tx F, and SI as shown in the table below.

The 4-g dose of mesalamine also gave consistent improvement in secondary efficacy parameters, namely the frequency of trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain, and urgency. The 4-g dose of mesalamine induced remission as assessed by endoscopic and symptomatic endpoints.

In some patients, the 2-g dose of mesalamine was observed to improve efficacy parameters measured. However, the 2-g dose gave inconsistent results in primary efficacy parameters across the two adequate and well controlled trials.

| Parameter Evaluated | Clinical Trial UC-1 | | | Clinical Trial UC-2 | | |
|---------------------|---------------------|-----------------------------|-----------------------------|---------------------|-----------------------------|-----------------------------|
| | PL (n = 90) | Mesalamine 4 g/day (n = 95) | Mesalamine 2 g/day (n = 97) | PL (n = 83) | Mesalamine 4 g/day (n = 85) | Mesalamine 2 g/day (n = 83) |
| PGA | 36% | 59%* | 57%* | 31% | 55%* | 41% |
| Tx F | 22% | 9%* | 18% | 31% | 9%* | 17%* |
| SI | -2.5 | -5.0* | -4.3* | -1.6 | -3.8* | -2.6 |
| Remission† | 12% | 26%* | 24%* | 12% | 27%* | 12% |

*p<0.05 vs placebo.

PGA: Physician Global Assessment: proportion of patients with complete or marked improvement.

Tx F: Treatment Failure: proportion of patients developing severe or fulminant UC requiring steroid therapy or hospitalization or worsening of the disease at 7 days of therapy, or lack of significant improvement by 14 days of therapy.

SI: Sigmoidoscopic Index: an objective measure of disease activity rated by a standard (15-point) scale that includes mucosal vascular pattern, erythema, friability, granularity/ulcerations, and mucopus: improvement over baseline.

†Defined as complete resolution of symptoms plus improvement of endoscopic endpoints. To be considered in remission, patients had a "1" score for one of the endoscopic components (mucosal vascular pattern, erythema, granularity, or friability) and "0" for the others.

INDICATIONS AND USAGE

Mesalamine extended-release capsules are indicated for the induction of remission and for the treatment of adult patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS

Mesalamine extended-release capsules are contraindicated in patients with known or suspected hypersensitivity to salicylates, aminosaliclylates, or any components of this medication.

PRECAUTIONS

Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and renal failure have been reported in patients given mesalamine extended-release capsules or other products that contain mesalamine or are converted to mesalamine.

Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on therapy with mesalamine extended-release capsules. Evaluate the risks and benefits of using mesalamine extended-release capsules in patients with known renal impairment or a history of renal disease or taking concomitant nephrotoxic drugs.

Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Symptoms include cramping, acute abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine extended-release capsules.

Hypersensitivity Reactions

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

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

Hepatic Failure

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in with the use of mesalamine (see **ADVERSE REACTIONS**). Discontinue mesalamine at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Photosensitivity

Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with 100% mesalamine content. Mesalamine-containing stones are radiotransparent and undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment.

Interference with Laboratory Tests

Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

Drug Interactions

No investigations of interactions between mesalamine and other drugs have been performed; however, the following drug-drug interactions have been reported for products containing mesalamine:

Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs), may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine and/or any other drugs known to cause myelotoxicity may increase the risk for blood disorders, bone marrow failure, and associated complications. If concomitant use of mesalamine and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50-kg person of average height (1.46 m² body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m²/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an *in vitro* Ames test and in an *in vivo* mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with mesalamine during controlled clinical trials.

Pregnancy

Teratogenic Effects

Published data from meta-analyses, cohort studies, and case series on the use of mesalamine during pregnancy have not reliably informed an association with mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no clear evidence that mesalamine exposure in early pregnancy is associated with an increased risk of major congenital malformations, including cardiac malformations. Published epidemiologic studies have important methodological limitations which hinder interpretation of the data, including inability to control for confounders, such as underlying maternal disease, maternal use of concomitant medications, and missing information on the dose and duration of use for mesalamine products. Mesalamine should only be used during pregnancy if the benefits outweigh the risks.

In animal reproduction studies, oral administration of mesalamine during organogenesis to pregnant rats at doses up to 1000 mg/kg/day (5900 mg/m²) and rabbits at doses of 800 mg/kg/day (6856 mg/m²) revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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Track : A09/07/2021, A12/07/2021,
A20/07/2021, A07/12/2021, A08/12/2021-II

SAP CODE : 5221720
ITF CODE : 05221720

Nonteratogenic Effects

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Nursing Mothers

Data from published literature report the presence of mesalamine and its metabolite, N- acetyl-5-aminosalicylic acid in human milk in small amounts with relative infant doses (RID) of 0.1% or less for mesalamine. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine.

There are reports of diarrhea observed in breastfed infants exposed to mesalamine. The effect of mesalamine on milk production is unknown. Exercise caution if mesalamine extended-release capsules are administered to a nursing woman and monitor breastfed infants for diarrhea.

In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 4.8 g daily. The average concentration of mesalamine in milk ranged from non-detectable to 0.5 mg/L. The average concentration of N-acetyl-5-aminosalicylic acid in milk ranged from 0.2 to 9.3 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 to

0.075 mg/kg/day of mesalamine (RID 0% to 0.1%) and 0.03 to 1.4 mg/kg/day of N-acetyl-5-aminosalicylic acid.

Pediatric Use

Safety and efficacy of mesalamine in pediatric patients have not been established.

Geriatric Use

Clinical trials of mesalamine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias (i.e., agranulocytosis, neutropenia, and pancytopenia) in patients receiving mesalamine-containing products such as mesalamine extended-release capsules who were 65 years or older compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with mesalamine extended-release capsules.

In general, consider the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy in elderly patients when prescribing mesalamine.

ADVERSE REACTIONS

In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received mesalamine therapy. Generally, mesalamine therapy was well tolerated. The most common events (i.e., greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).

In two domestic placebo-controlled trials involving over 600 patients with ulcerative colitis, adverse events were fewer in mesalamine-treated patients than in the placebo group (mesalamine 14% vs placebo 18%) and were not dose-related. Events occurring in more than 1% are shown in the table below. Of these, only nausea and vomiting were more frequent in the mesalamine group. Withdrawal from therapy due to adverse events was more common on placebo than mesalamine (7% vs 4%).

| Table 1. Adverse Events Occurring in More than 1% of Either Placebo or Mesalamine Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (Mesalamine Comparison to Placebo) | | |
|---|-----------------------|--------------------|
| Event | Mesalamine n = 451 | Placebo n = 173 |
| Diarrhea | 16 (3.5%) | 13 (7.5%) |
| Headache | 10 (2.2%) | 6 (3.5%) |
| Nausea | 14 (3.1%) | ---- |
| Abdominal Pain | 5 (1.1%) | 7 (4.0%) |
| Melena (Bloody Diarrhea) | 4 (0.9%) | 6 (3.5%) |
| Rash | 6 (1.3%) | 2 (1.2%) |
| Anorexia | 5 (1.1%) | 2 (1.2%) |
| Fever | 4 (0.9%) | 2 (1.2%) |
| Rectal Urgency | 1 (0.2%) | 4 (2.3%) |
| Nausea and Vomiting | 5 (1.1%) | ---- |
| Worsening of Ulcerative Colitis | 2 (0.4%) | 2 (1.2%) |
| Acne | 1 (0.2%) | 2 (1.2%) |

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematological, liver, and kidney function.

The following adverse events, presented by body system, were reported infrequently (i.e., less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to mesalamine has not been established.

Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliasis, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst

Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocytopenia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.

Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with mesalamine therapy.

Postmarketing Reports

The following events have been identified during post-approval use of the mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal: Reports of hepatotoxicity, including elevated liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), hepatitis, jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.

Other: anaphylactic reaction, SJS/TEN, DRESS, AGEF, pleurisy/pleuritis, pneumonitis, granulocytopenia, systemic lupus erythematosus, lupus-like syndrome, acute renal failure, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), chronic renal failure, nephrogenic diabetes insipidus, nephrolithiasis, intracranial hypertension, angioedema, and oligospermia (reversible).

OVERDOSAGE

Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may be possible, such as: nausea, vomiting, abdominal pain, tachypnea, hyperpnea, tinnitus, and neurologic symptoms (headache, dizziness, confusion, seizures). Severe intoxication with salicylates may lead to electrolyte and blood-pH imbalance and potentially to other organ (e.g., renal and liver) damage.

Treatment of Overdosage: There is no specific antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdose and may include gastrointestinal tract decontamination to prevent further absorption. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy and maintain adequate renal function.

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis in adults is 1 g (2 mesalamine extended-release 500-mg capsules) 4 times a day for a total daily dosage of 4 g. Treatment duration in controlled trials was up to 8 weeks.

Mesalamine extended-release capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.

Drink an adequate amount of fluids.

Safety and efficacy of mesalamine in pediatric patients have not been established.

HOW SUPPLIED

Mesalamine extended-release capsules, USP 500 mg are supplied in bottles of 120 capsules with child-resistant closure (NDC 63304-089-13). Each dark blue capsule contains 500 mg of mesalamine, USP in extended-release pellets.

Mesalamine extended-release capsules, USP 500 mg are hard gelatin having dark blue cap and body with "RL36" printed on both cap and body in black ink containing off-white to light yellowish brown to dark yellowish brown colored pellets.

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Preserve in tight, light-resistant containers.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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