

Mesalamine Delayed-Release Tablets, USP

2102248

2D Code

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

-----RECENT MAJOR CHANGES-----
Warnings and Precautions, Renal Impairment (5.1) 11/2022

-----INDICATIONS AND USAGE-----
Mesalamine delayed-release tablet is an aminosalicilate indicated for the:
• induction and maintenance of remission in adult patients with mildly to moderately active ulcerative colitis. (1)

-----DOSAGE AND ADMINISTRATION-----
Administration Instructions
• Evaluate renal function prior to initiation of mesalamine delayed-release tablets and periodically while on therapy. (2, 5.1)
• Swallow mesalamine delayed-release tablets whole; do not split or crush. (2)
• Administer mesalamine delayed-release tablets with food. (2)
• Drink an adequate amount of fluids. (2, 5.8)

Recommended Dosage in Adults
• For induction of remission: 2.4 g to 4.8 g (two to four 1.2-g tablets) once daily. (2)
• For maintenance of remission: 2.4 g (two 1.2-g tablets) once daily. (2)

-----DOSAGE FORMS AND STRENGTHS-----
Delayed-Release Tablets: 1.2 g (3)

-----CONTRAINDICATIONS-----
Known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of mesalamine. (4)

-----WARNINGS AND PRECAUTIONS-----
• **Renal Impairment:** Assess renal function at the beginning of treatment and periodically during treatment. Evaluate the risks and benefits of mesalamine in patients with known renal impairment or taking nephrotoxic drugs. Discontinue mesalamine if renal function deteriorates while on therapy. (5.1, 7.1, 8.6)
• **Mesalamine-Induced Acute Intolerance Syndrome:** Symptoms may be difficult to distinguish from an ulcerative colitis exacerbation. Monitor for worsening symptoms while on treatment. Discontinue treatment if acute intolerance syndrome is suspected. (5.2)
• **Hypersensitivity Reactions, including myocarditis and pericarditis:** Evaluate patients immediately and discontinue mesalamine if a hypersensitivity reaction is suspected. (5.3)

- **Hepatic Failure:** Evaluate the risks and benefits of using mesalamine in patients with known liver impairment. (5.4)
- **Severe Cutaneous Adverse Reactions:** Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
- **Upper Gastrointestinal Tract Obstruction:** Avoid in patients with pyloric stenosis or other organic or functional obstruction. (5.6)
- **Photosensitivity:** Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors. (5.7)
- **Nephrolithiasis:** Cases of nephrolithiasis have been reported with the use of mesalamine. Mesalamine-containing stones are undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment. (5.8)
- **Interference With Laboratory Tests:** Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. (5.9)

-----ADVERSE REACTIONS-----
Most common adverse reactions in:
• adults (≥ 2%) are headache, flatulence, liver function test abnormal, abdominal pain, and diarrhea. (6.1)

• To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

-----USE IN SPECIFIC POPULATIONS-----
Geriatric Patients: Increased risk of blood dyscrasias; monitor complete blood cell counts and platelet counts. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2022

Pediatric use information is approved for Takeda Pharmaceuticals U.S.A., Inc.'s LIALDA (mesalamine) delayed-release tablets. However, due to Takeda Pharmaceuticals U.S.A., Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Mesalamine delayed-release tablets are indicated for the:

- induction and maintenance of remission in adult patients with mildly to moderately active ulcerative colitis.
- Pediatric use information is approved for Takeda Pharmaceuticals U.S.A., Inc.'s LIALDA (mesalamine) delayed-release tablets. However, due to Takeda Pharmaceuticals U.S.A., Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.*

2 DOSAGE AND ADMINISTRATION

Administration Instructions

- Evaluate renal function prior to initiation of mesalamine delayed-release tablets and periodically while on therapy.
- Swallow mesalamine delayed-release tablets whole; do not split or crush.
- Administer mesalamine delayed-release tablets with food. *[see Clinical Pharmacology (12.3)].*
- Drink an adequate amount of fluids. *[see Warnings and Precautions (5.8)].*

Adults

- The recommended dosage for the induction of remission in adult patients with mildly to moderately active ulcerative colitis is 2.4 g to 4.8 g (two to four 1.2-g tablets) taken once daily.
- The recommended dosage for the maintenance of remission is 2.4 g (two 1.2-g tablets) taken once daily.

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3 DOSAGE FORMS AND STRENGTHS

The reddish-brown, oval-shaped, enteric-coated tablets containing 1.2 g mesalamine is imprinted with "M19" in black color on one side and plain on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as mesalamine that contain mesalamine or are converted to mesalamine. In animal studies, the kidney was the principal organ of mesalamine toxicity. *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.2)].*

Evaluate renal function prior to initiation of mesalamine therapy and periodically while on therapy. Evaluate the risks and benefits of using mesalamine in patients with known renal impairment, history of renal disease, or taking concomitant nephrotoxic drugs. Discontinue mesalamine if renal function deteriorates while on therapy. *[see Drug Interactions (7.1), Use in Specific Populations (8.6)].*

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain, and bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some of these patients may have a similar reaction to mesalamine delayed-release tablets 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 or symptoms cannot be established.

5.4 Hepatic Failure

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

5.5 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 with the use of mesalamine. *[see Adverse Reactions (6.2)].* Discontinue mesalamine at the first appearance of signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

5.6 Upper Gastrointestinal Tract Obstruction

Pyloric stenosis or other organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of mesalamine, which would delay mesalamine release in the colon. Avoid mesalamine in patients at risk of upper gastrointestinal tract obstruction.

5.7 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.

5.8 Nephrolithiasis

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

5.9 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 the main metabolite of mesalamine, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Renal impairment, including renal failure. *[see Warnings and Precautions (5.1)]*
- Mesalamine-induced acute intolerance syndrome. *[see Warnings and Precautions (5.2)]*
- Hypersensitivity reactions. *[see Warnings and Precautions (5.3)]*
- Hepatic failure. *[see Warnings and Precautions (5.4)]*
- Severe cutaneous adverse reactions. *[see Warnings and Precautions (5.5)]*
- Upper gastrointestinal tract obstruction. *[see Warnings and Precautions (5.6)]*
- Photosensitivity. *[see Warnings and Precautions (5.7)]*
- Nephrolithiasis. *[see Warnings and Precautions (5.8)]*

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.

Adults

Induction

The most common adverse reactions occurring in at least 1% of mesalamine- or placebo-treated adult patients with mildly to moderately active ulcerative colitis in two eight-week, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2) *[see Clinical Studies (14.1)]* are listed in Table 2.

Table 2: Adverse Reactions* in Two Eight-Week, Placebo-Controlled Trials of Induction Therapy (Study 1 and Study 2) in Adults with Mildly to Moderately Active Ulcerative Colitis

Adverse Reaction	Mesalamine 2.4 g once daily (n=177)	Mesalamine 4.8 g once daily (n=179)	Placebo (n=179)
Headache	6%	3%	< 1%
Flatulence	4%	3%	3%
Liver Function Test Abnormal	< 1%	2%	1%
Alopecia	0	1%	0
Pruritus	< 1%	1%	1%

* Reported in at least 1% of patients in at least one mesalamine group and greater than placebo

Pancreatitis occurred in less than 1% of patients during induction in clinical trials and resulted in discontinuation of therapy with mesalamine in patients experiencing this event.

Maintenance of Remission

A mesalamine dosage of 2.4 g/day, administered as either 1.2 g twice daily or 2.4 g once daily, was evaluated for safety in three maintenance trials in patients with mildly to moderately active ulcerative colitis: a 6-month double-blind, active-controlled study (Study 3) *[see Clinical Studies (14.1)]* and two 12- to 14-month open-label studies. The most common adverse reactions with mesalamine in these maintenance trials are listed in Table 3.

Table 3: Adverse Reactions* in Three Trials of Maintenance of Remission in Adults with Ulcerative Colitis

Adverse Reaction	Mesalamine 2.4 g/day (n=1082)
Headache	3%
Liver function test abnormal	2%
Abdominal pain	2%
Diarrhea	2%
Abdominal distension	1%
Abdominal pain upper	1%
Dyspepsia	1%
Back pain	1%
Rash	1%
Arthralgia	1%
Fatigue	1%
Hypertension	1%

* Reported in at least 1% of patients

Administered either as 1.2 g twice daily or 2.4 g once daily

The following adverse reactions, presented by body system, were reported in less than 1% of mesalamine-treated patients with ulcerative colitis in either induction or maintenance trials:

Cardiac Disorder: tachycardia

Ear and Labyrinth Disorders: ear pain

Gastrointestinal Disorders: abdominal distention, colitis, diarrhea, flatulence, nausea, pancreatitis, rectal polyp, vomiting

General Disorders and Administrative Site Disorders: asthenia, face edema, fatigue, pyrexia

Investigations: decreased platelet count

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain

Nervous System Disorders: dizziness, somnolence, tremor

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain

Skin and Subcutaneous Tissue Disorders: acne, prurigo, rash, alopecia, pruritus, urticaria

Vascular Disorders: hypertension, hypotension

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of mesalamine or 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: lupus-like syndrome, drug fever

Cardiac Disorders: pericarditis, pericardial effusion, myocarditis. *[see Warnings and Precautions (5.3)]*

Gastrointestinal: cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer

Hepatic: jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, hepatotoxicity, Kawasaki-like syndrome including changes in liver enzymes

Hematologic: agranulocytosis, aplastic anemia

Immune System Disorders: anaphylactic reaction, angioedema

Musculoskeletal and Connective Tissue Disorders: myalgia, lupus-like syndrome

Neurological/Psychiatric: peripheral neuropathy, Guillain-Barré syndrome, transverse myelitis, intracranial hypertension

Renal Disorders: renal failure, interstitial nephritis, nephrogenic diabetes insipidus, nephrolithiasis. *[see Warnings and Precautions (5.1, 5.8)]*

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), pleurisy/pleuritis

Skin: psoriasis, pyoderma gangrenosum, erythema nodosum, photosensitivity, SJS/TEN, DRESS, and AGEP. *[see Warnings and Precautions (5.5)]*

Urogenital: reversible oligospermia

7 DRUG INTERACTIONS

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

7.2 Azathioprine and 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.

7.3 Interference with Urinary Normetanephrine Measurements

Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. *[see Warnings and Precautions (5.9)].* Consider an alternative, selective assay for normetanephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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. *(see Data)*. There are adverse effects on maternal and fetal outcomes associated with ulcerative colitis in pregnancy. *(see Clinical Considerations)*.

In animal reproduction studies, there were no adverse developmental outcomes with administration of oral mesalamine during organogenesis to pregnant rats and rabbits at doses 1.8 and 2.9 times, respectively, the maximum recommended human dose. *(see Data)*.

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.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

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.

Data

Human Data

Published data from meta-analyses, cohort studies, and case series on the use of mesalamine during early pregnancy (first trimester) and throughout pregnancy have not reliably informed an association of 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.

Animal Data

Reproduction studies with mesalamine during organogenesis have been performed in rats at doses up to 1000 mg/kg/day (1.8 times

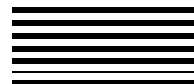
Dimensions: 200 x 500 mm

Pharma Code: Front-221 & Back-222

Spec.: Printed on 40 GSM Bible paper, front & back side printing

Note: Pharma code position and Orientation are tentative, will be changed based on folding size.

No of Colours: 01 - Pantone Black C



the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of harm to the fetus due to mesalamine.

8.2 Lactation

Risk Summary

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 (see Data). There are case reports of diarrhea in breastfed infants exposed to mesalamine (see Clinical Considerations). There is no information on the effects of the drug on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of mesalamine to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mesalamine and any potential adverse effects on the breastfed child from mesalamine or from the underlying maternal condition.

Clinical Considerations

Advise the caregiver to monitor the breastfed infant for diarrhea.

Data

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

8.4 Pediatric Use

The safety and effectiveness of mesalamine have not been established in patients weighing less than 24 kg.

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8.5 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 who were 65 years or older who were taking mesalamine-containing products such as mesalamine compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with mesalamine.

Systemic exposures are increased in elderly subjects (see Clinical Pharmacology (12.3)).

In general, consider the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients when prescribing mesalamine. Consider starting at the low end of the dosing range for induction in elderly patients (see Dosage and Administration (2), Use in Specific Populations (8.6)).

8.6 Renal Impairment

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

10 OVERDOSAGE

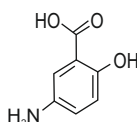
Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may include nausea, vomiting, abdominal pain, tachypnea, hyperpernea, tinnitus, and neurologic symptoms (headache, dizziness, confusion, seizures). Severe intoxication with salicylates may lead to electrolyte and blood pH imbalance, and potentially end organ (e.g., renal and liver) damage.

There is no specific known 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.

Mesalamine is a pH-dependent, delayed-release product and this factor should be considered when treating a suspected overdose.

11 DESCRIPTION

Each mesalamine delayed-release tablet, USP for oral administration contains 1.2 g 5-aminosalicylic acid (5-ASA; mesalamine), an anti-inflammatory agent. Mesalamine also has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular formula: C₇H₇NO₃

Molecular weight: 153.14

The tablet is coated with a pH-dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients and provides for extended release of mesalamine.

The inactive ingredients of mesalamine delayed-release tablets, USP are colloidal silicon dioxide, ferric oxide, hypromellose, magnesium stearate, methacrylic acid and methyl methacrylate copolymer, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, titanium dioxide, triethyl citrate, the imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol and shellac.

FDA approved dissolution test specifications differ from USP

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is not fully understood, but it appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxigenase pathways, is increased in patients with ulcerative colitis, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

12.3 Pharmacokinetics

Absorption

The total absorption of mesalamine from mesalamine 2.4 g or 4.8 g given once daily for 14 days to healthy subjects was found to be approximately 21% to 22% of the administered dose.

Gamma-scintigraphy studies have shown that a single dose of mesalamine 1.2 g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy subjects. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed through this region of the gastrointestinal tract.

In a single-dose study, mesalamine 1.2 g, 2.4 g, and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9 to 12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 4).

Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2 g and 4.8 g mesalamine. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionally between 1.2 g and 2.4 g and sub-proportionally between 2.4 g and 4.8 g of mesalamine, with the dose normalized value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means.

Table 4: Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of Mesalamine Under Fasting Conditions

Parameter* of Mesalamine	Mesalamine 1.2 g (N=47)	Mesalamine 2.4 g (N=48)	Mesalamine 4.8 g (N=48)
AUC ₀₋₈ (ng·h/mL)	9039 (5054)	20538 (12980)	41434 (26640)
AUC _{0-∞} (ng·h/mL)	9578 (5214)	21084 (13185)	44775 (30302)
C _{max} (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T _{max} [†] (h)	9.0 [†] (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
T _{1/2} [†] (h)	2.0 [†] (0.8-0.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
T _{1/2} (h) (Terminal Phase)	8.56 [†] (6.38)	7.05 [†] (5.54)	7.25 [†] (8.32)

* Arithmetic mean of parameter values are presented except for T_{max} and T_{1/2}.

[†] N=43, N=27, N=36, [†]Median (min, max), N=46, N=33

Food Effects

Administration of a single dose of mesalamine 4.8 g with a high-fat meal resulted in further delay in absorption, and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high-fat meal increased systemic exposure of mesalamine (mean C_{max}; increased 91%; mean AUC; increased 16%) compared to results in the fasted state. Mesalamine was administered with food in the controlled clinical trials (see Dosage and Administration (2)).

In a single and multiple dose pharmacokinetic study of mesalamine, 2.4 g or 4.8 g was administered once daily with standard meals to 28 healthy subjects per dose group. Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was achieved generally by 2 days after dosing. Mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

Distribution

Mesalamine is approximately 43% bound to plasma proteins at the concentration of 2.5 mcg/mL.

Elimination

Metabolism

The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.

Excretion

Excretion of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation); however, there is also limited excretion of the parent drug in urine. Of the approximately 21% to 22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The mean renal clearance (CL_r) in adults ranged from 1.8 L/h to 2.9 L/h following single dose administration and ranged from 5.5 L/h to 6.4 L/h after a multiple dosing for 14 days. The apparent terminal half-lives for mesalamine and its major metabolite after administration of mesalamine 2.4 g and 4.8 g were, on average, 7 to 9 hours and 8 to 12 hours, respectively.

Systemic exposures in adult subjects were inversely correlated with renal function as assessed by estimated creatinine clearance (see Use in Specific Populations (8.6)).

Specific Populations

Geriatric Patients

In a single-dose pharmacokinetic study of mesalamine, 4.8 g was administered in the fasted state to 71 healthy male and female subjects (28 young (18 to 35 years); 28 elderly (65 to 75 years); 15 elderly (> 75 years)). Increased age resulted in increased systemic exposure (approximately 2-fold in C_{max}) to mesalamine and its metabolite N-acetyl-5-aminosalicylic acid. Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability.

Table 5: Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of Mesalamine 4.8 g under Fasting Conditions to Young and Elderly Subjects

Parameter of 5-ASA	Young Subjects (18 to 35 years) (N=28)	Elderly Subjects (65 to 75 years) (N=28)	Elderly Subjects (75 years and older) (N=15)
AUC ₀₋₈ (ng·h/mL)	51570 (23870)	73001 (42608)	65820 (25283)
AUC _{0-∞} (ng·h/mL)	58057* (22429)	89612* (40596)	63067* (22531)
C _{max} (ng/mL)	2243 (1410)	4999 (4381)	4832 (4383)
t _{max} [†] (h)	22.0 (5.98-48.0)	12.5 (4.00-36.0)	16.0 (4.00-26.0)
t _{1/2} [†] (h)	2 (1-6)	2 (1-4)	2 (2-4)
t _{1/2} (h), terminal phase	5.68* (2.83)	9.68 [†] (7.47)	8.67 [†] (5.84)
Renal clearance (L/h)	2.05 (1.33)	2.04 (1.16)	2.13 (1.20)

Arithmetic mean (SD) data are presented, N = Number of subjects; 5-ASA = 5-aminosalicylic acid

* N=15, N=16, N=13, [†]Median (min-max)

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Drug Interaction Studies

The potential effect of mesalamine (4.8 g given once daily) on the pharmacokinetics of four commonly used antibiotics were evaluated in healthy subjects. The four antibiotics studied and their dosing regimens were as follows: amoxicillin (single 500 mg dose), ciprofloxacin XR (single 500-mg dose), metronidazole (750 mg twice daily for 3.5 days), and sulfamethoxazole/trimethoprim (800 mg/160 mg twice daily for 3.5 days). The change in C_{max} and AUC of amoxicillin, ciprofloxacin, and metronidazole when they were co-administered with mesalamine were all 3% or less. There was an increase of 12% in C_{max} and an increase of 15% in AUC of sulfamethoxazole when sulfamethoxazole/trimethoprim was coadministered with mesalamine. Coadministration of mesalamine did not result in clinically significant changes in the pharmacokinetics of any of the four antibiotics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week dietary carcinogenicity study in CD-1 mice, mesalamine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of mesalamine. Furthermore, 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 is 1.4 times the recommended human dose (based on a body surface area comparison) of mesalamine.

Mutagenesis

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

Impairment of Fertility

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 (0.7 times the maximum recommended human dose based on a body surface area comparison).

13.2 Animal Toxicology and/or Pharmacology

In animal studies with mesalamine, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

14 CLINICAL STUDIES

14.1 Adults with Mildly to Moderately Active Ulcerative Colitis

Induction of Remission

Two similarly designed, randomized, double-blind, placebo-controlled trials (Study 1, NCT00503243 and Study 2, NCT00548574) were conducted in 517 adult patients with mildly to moderately active ulcerative colitis. The study population was primarily Caucasian (80%), had a mean age of 42 years (6% age 65 years or older), and was approximately 50% male. Both studies used mesalamine dosages of 2.4 g and 4.8 g administered once daily for 8 weeks, except in Study 1 the 2.4 g dosage was administered as two divided doses (i.e., 1.2 g twice daily). The primary efficacy endpoint in both trials was to compare the percentage of patients in remission after 8 weeks of treatment for the mesalamine treatment groups versus placebo. Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) of \leq 1, with scores of zero for rectal bleeding and for stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

In both studies, the mesalamine dosages of 2.4 g and 4.8 g once daily demonstrated superiority over placebo in the primary efficacy endpoint (Table 6). Both mesalamine dosages also provided consistent benefit in secondary efficacy parameters, including clinical improvement, clinical remission, and sigmoidoscopic improvement. Both mesalamine dosages had similar efficacy profiles.

Table 6: Proportion of Adult Patients with Mildly to Moderately Active Ulcerative Colitis in Remission at Week 8 in Two Double-Blind Placebo-Controlled Induction Trials

Dose	Study 1 (n=262) n/N (%)	Study 2 (n=255) n/N (%)
Mesalamine 2.4 g/day	30/88 (34)	34/84 (41)
Mesalamine 4.8 g/day	26/89 (29)	35/85 (41)
Placebo	11/85 (13)	19/86 (22)

Maintenance of Remission

A multicenter, randomized, double-blind, active comparator study (Study 3, NCT00151892) was conducted in a total of 826 adult patients in remission from ulcerative colitis. Patients were randomized in a 1:1 ratio to receive either mesalamine 2.4 g administered once daily or another mesalamine delayed-release product administered as 0.8 g twice daily. The study population had a mean age of 45 years (8% age 65 years or older), were 52% male, and were primarily Caucasian (64%).

Maintenance of remission was assessed using a modified UC-DAI. For this trial, maintenance of remission was based on maintaining endoscopic remission defined as a modified UC-DAI endoscopy subscore of \leq 1. An endoscopy subscore of 0 represented normal mucosal appearance with intact vascular pattern and no friability or granulation. For this trial the endoscopy score definition of 1 (mild disease) was modified such that it could include erythema, decreased vascular pattern, and minimal granularity; however, it could not include friability.

The proportion of patients who maintained remission at Month 6 in this study using mesalamine 2.4 g once daily (84%) was similar to the comparator (82%).

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16 HOW SUPPLIED/STORAGE AND HANDLING

Mesalamine delayed-release tablets, USP are available as reddish-brown, oval-shaped, enteric-coated tablets containing 1.2 g mesalamine is imprinted with "M19" in black color on one side and plain on other side supplied in:

HDPE Bottle with a child-resistant closure of 120 delayed-release tablets NDC 31722-043-12

HDPE Bottle with a child-resistant closure of 500 delayed-release tablets NDC 31722-043-05

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Renal Impairment

Inform patients that mesalamine delayed-release tablets may decrease their renal function, especially if they have known renal impairment or are taking nephrotoxic drugs, and periodic monitoring of renal function will be performed while they are on therapy. Advise patients to complete all blood tests ordered by their healthcare provider (see Warnings and Precautions (5.1)).

Mesalamine-Induced Acute Intolerance Syndrome and Other Hypersensitivity Reactions

Advise patients to stop taking mesalamine delayed-release tablets and report to their healthcare provider if they experience new or worsening symptoms of acute intolerance syndrome (cramping, abdominal pain, bloody diarrhea, fever, headache, and rash) or other symptoms suggestive of mesalamine-induced hypersensitivity (see Warnings and Precautions (5.2, 5.3)).

Hepatic Failure

Advise patients with known liver disease to contact their healthcare provider if they experience signs or symptoms of worsening liver function (see Warnings and Precautions (5.4)).

Severe Cutaneous Adverse Reactions

Inform patients of the signs and symptoms of severe cutaneous adverse reactions. Instruct patients to stop taking mesalamine delayed-release tablets and report to their healthcare provider at first appearance of a severe cutaneous adverse reaction or other sign of hypersensitivity (see Warnings and Precautions (5.5)).

Upper Gastrointestinal Tract Obstruction

Advise patients to contact their healthcare provider if they experience signs and symptoms of upper gastrointestinal tract obstruction (see Warnings and Precautions (5.6)).

Photosensitivity

Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors (see Warnings and Precautions (5.7)).

Nephrolithiasis

Instruct patients to drink an adequate amount of fluids during treatment in order to minimize the risk of kidney stone formation and to contact their healthcare provider if they experience signs or symptoms of a kidney stone (e.g., severe side or back pain, blood in the urine) (see Warnings and Precautions (5.8)).

Blood Disorders

Inform elderly patients and those taking azathioprine or 6-mercaptopurine of the risk for blood disorders and the need for periodic monitoring of complete blood cell counts and platelet counts while on therapy. Advise patients to complete all blood tests ordered by their healthcare provider (see Drug Interactions (7.2), Use in Specific Populations (8.5)).

Administration

Instruct patients:

- Swallow mesalamine delayed-release tablets whole; do not split or crush.
- Take mesalamine delayed-release tablets with food (see Clinical Pharmacology (12.3)).
- Drink an adequate amount of fluids (see Warnings and Precautions (5.8)).



Manufactured by:
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By: Annora Pharma Pvt. Ltd.
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Pharma Code: Front-221 & Back-222

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Note: Pharma code position and Orientation are tentative, will be changed based on folding size.

No of Colours: 01 - Pantone Black C