PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

MEZAVANT®

mesalamine

Tablets (delayed and extended release), 1.2 g, Oral use

Intestinal Anti-inflammatory Agent

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General	08-2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MEZAVANT® (mesalamine delayed- and extended-release tablets) is indicated for:

- Induction of remission (clinical and endoscopic) in patients with active, mild to moderate ulcerative colitis.
- Maintenance of clinical and endoscopic remission (mucosal healing) in patients with ulcerative colitis.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Clinical trials of MEZAVANT did not include sufficient numbers of patients aged 65 years and over to determine whether elderly patients respond differently from younger patients. Evidence from the pharmacokinetic study indicates that systemic exposure to mesalazine and its metabolite N-acetyl-5-aminosalicylic acid in geriatrics subjects is up to 2-fold higher than in adult subjects (18-35 years). The potential impact on the safe use of MEZAVANT in the elderly population in clinical practice should be considered (7.1.4 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; 10.3 Pharmacokinetics, Absorption).

2 CONTRAINDICATIONS

MEZAVANT is contraindicated in:

- Patients who are hypersensitive to any salicylates (including mesalamine) or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Patients with severe renal impairment (GFR <30 mL/min/1.73 m2) and/or severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Administration of a single dose of MEZAVANT 4.8 g with a high-fat meal in healthy volunteers increased systemic exposure of mesalamine compared to results in the fasted state; consideration should be given to this observation when prescribing to patients expected to consume high fat meals. However, MEZAVANT was administered with food, part of an unrestricted diet, in the pivotal Phase 3 trials (see 9.5 DRUG INTERACTIONS, Drug-Food Interactions and 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).
- In patients with mild to moderate renal impairment, mesalamine products should be used only if the benefits outweigh the risks. Therefore, caution should be exercised, and it is

recommended that all patients have an evaluation of renal function prior to initiation of therapy, and periodically while on treatment (see 7 WARNINGS AND PRECAUTIONS, Renal).

4.2 Recommended Dose and Dosage Adjustment

MEZAVANT is intended for once daily, oral administration with food.

The recommended dose for the induction of remission in patients with mild to moderate ulcerative colitis is two to four 1.2 g tablets to be taken once daily for a total daily dose of 2.4 to 4.8 g.

The recommended dose for the maintenance of clinical and endoscopic remission (mucosal healing) is two 1.2 g tablets to be taken once daily for a total daily dose of 2.4 g.

As for tablets needing to be swallowed whole, consideration should be given to the ability to swallow the intact tablet.

Pediatrics:

Health Canada has not authorized an indication for pediatric use.

Geriatrics:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance. The potential impact on the safe use of MEZAVANT in the elderly population in clinical practice should be considered (see 7 WARNINGS AND PRECAUTIONS, Renal; 7.1.4 Special Populations, Geriatrics; and 10.3 Pharmacokinetics Special Populations and Conditions).

4.4 Administration

The tablets should be swallowed whole with liquid and should not be crushed or chewed taking care not to break the outer coating. The outer coating is designed to remain intact until at least pH 7, normally in the terminal ileum, to protect the active ingredient, mesalamine, and ensure its availability throughout the colon.

4.5 Missed Dose

If a dose of this medication has been missed, it should be skipped and taken as usual the next day.

5 OVERDOSAGE

MEZAVANT is an aminosalicylate, and symptoms of salicylate toxicity may include confusion, diarrhea, drowsiness, headache, hyperventilation, sweating, tinnitus, vertigo, and vomiting. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration.

Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy. Maintain adequate renal function.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral use	Tablet (delayed and extended release), 1.2 g	carnauba wax, magnesium stearate, methacrylic acid – methyl methacrylate copolymer (1:1), methacrylic acid – methyl methacrylate copolymer (1:2), polyethylene glycol (macrogol) 6000, red ferric oxide (E172), silica (colloidal hydrated), sodium carboxymethylcellulose, sodium starch glycolate (type A), stearic acid, talc, titanium dioxide (E171) and triethylcitrate

MEZAVANT tablets are available as red-brown ellipsoidal film-coated tablets containing 1.2 g of mesalamine, and debossed on one side with S476.

The MEZAVANT delayed- and extended-release tablet contains a core of 1200 mg mesalamine (5-aminosalicylic acid; 5-ASA), formulated with a matrix of lipophilic and hydrophilic excipients. The tablet is coated with a gastro-resistant film of methacrylic acid – methyl methacrylate copolymer (1:1) and methacrylic acid – methyl methacrylate copolymer (1:2) (MMX Multi Matrix System®), which are designed to delay the initial release of mesalamine until exposure to approximately pH 7 and above, normally in the terminal ileum. A consistent and sustained release was observed across the pH range 6.8 to 7.2. The combination of the matrix of lipophilic and hydrophilic excipients (MMX Multi Matrix System®) and gastro-resistant coating facilitate the delayed and extended delivery of effective concentrations of mesalamine through the entire colon with limited systemic absorption.

MEZAVANT tablets do not contain gluten, lactose or phthalates.

MEZAVANT tablets are supplied in opaque high-density polyethylene (HDPE) bottle of 120 tablets with child-resistant closure.

7 WARNINGS AND PRECAUTIONS

General

Mesalamine products should not be used in patients with urinary tract obstruction, unless the expected benefit outweighs the risks. Extreme caution should be exercised and renal/urinary function should be closely monitored.

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. 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, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required.

In patients with mild to moderate impaired liver function, mesalamine products should be used only if

the expected benefits outweigh the risks to the patient. Caution should be exercised (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Carcinogenesis and Mutagenesis

Preclinical carcinogenicity and mutagenicity studies demonstrated mesalamine was not tumorigenic and there was no evidence of mutagenicity (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

Mesalamine induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely with MEZAVANT and other mesalamine-containing preparations. Caution should be taken in prescribing this medication to patients with conditions predisposing to the development of myocarditis or pericarditis.

Gastrointestinal

Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of the product.

Mesalamine products should not be used in patients with existing gastric or duodenal ulcer, unless the expected benefit outweighs the risks. Extreme caution should be exercised and adequate care given to those patients.

Acute intolerance syndrome: See 7.WARNINGS AND PRECAUTIONS/General.

Hematologic

Following mesalamine treatment, serious blood dyscrasias (including myelosuppression) have been reported rarely. The risk is further increased when mesalamine products are used concomitantly with 6-mercaptopurine or azathioprine (see 9 DRUG INTERACTIONS, Drug-Drug Interactions). If the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat, haematological investigations should be performed. If there is suspicion of blood dyscrasia, mesalamine treatment should be discontinued.

Hepatic/Biliary/Pancreatic

There have been reports of hepatic failure and increased liver enzymes in patients with pre- existing liver disease when treated with mesalamine products. Therefore, mesalamine is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and mesalamine products should only be used if the expected benefit clearly outweighs the risks to the patients. Appropriate assessment and monitoring of liver function should be performed.

Renal

Reports of renal impairment, including minimal change nephropathy, acute or chronic interstitial nephritis and renal failure have been associated with mesalamine products and pro-drugs of mesalamine.

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. Ensure adequate fluid intake during treatment.

Mesalamine is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, caution should be exercised and mesalamine products should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment based on clinical judgment taking baseline renal function into account (see 10.3 Pharmacokinetics). Treatment should be discontinued if renal function deteriorates.

Respiratory

Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions with mesalamine products and should be closely monitored.

Skin

Photosensitivity: Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions.

Hypersensitivity:

Use of mesalazine has been associated with the following serious and life-threatening skin reactions:

- Drug reaction with eosinophilia and systemic symptoms (DRESS),
- Severe cutaneous adverse reactions (SCARs),
- Stevens-Johnson syndrome (SJS),
- Toxic epidermal necrolysis (TEN).

At the time of prescription, patients should be informed of the signs and symptoms of SJS, TEN and DRESS, and be advised to monitor closely for skin reactions. Discontinue mesalazine at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of mesalamine in pregnant women. Mesalamine is known to cross the placental barrier. Premature labor, congenital malformations, and other adverse pregnancy outcomes (including serious events such as ectrodactyly, oligohydramnios, congenital nephrotic syndrome, and fetal tachycardia) were reported in infants born to mothers who were exposed to mesalamine during pregnancy. One case each of fetal anemia and hydrops fetalis were also reported in one infant. MEZAVANT should therefore only be used during pregnancy if the benefits outweigh the risks.

7.1.2 Breast-feeding

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. There is limited experience in breastfeeding women using mesalamine. Serious cases of diarrhea has been reported in breastfed infants of mothers exposed to mesalamine.

When MEZAVANT is used in nursing women, infants should be monitored for changes in stool consistency as hypersensitivity reactions manifested as diarrhea in the infants have been reported. If the infant develops diarrhea, breastfeeding should be discontinued. Caution should be exercised if MEZAVANT is administered to a nursing mother and used only if the benefits outweigh the risks.

7.1.3 Pediatrics

Safety and effectiveness of MEZAVANT in pediatric patients who are less than 18 years of age have not been established.

7.1.4 Geriatrics

The potential impact on the safe use of MEZAVANT in the elderly population in clinical practice should be considered. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy(see 7 WARNINGS AND PRECAUTIONS, Renal and 10.3 Pharmacokinetics)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

MEZAVANT tablets have been evaluated in 1368 ulcerative colitis patients in controlled and open label studies.

In the pooled safety analysis of patients with ulcerative colitis who participated in the clinical studies, the majority of subjects did not experience adverse drug reactions associated with MEZAVANT. Of the events reported, the majority were mild or moderate in severity. The most frequently reported adverse drug reactions within the pooled safety analysis of the ulcerative colitis patient clinical studies were ulcerative colitis, headache, abdominal pain, liver function test abnormal, diarrhea and nausea.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Induction of Remission, Including Clinical Remission and Mucosal Healing

In two 8-week double blind placebo-controlled clinical studies involving 621 (ITT Population) (Study SPD476-301 and SPD476-302) mild to moderate ulcerative colitis patients, 356 received 2.4 g/day or 4.8 g/day MEZAVANT tablets. More adverse events occurred in the placebo group (119) than in each of the MEZAVANT treatment groups (109 in 2.4 g/day, 92 in 4.8 g/day). The most common adverse events with MEZAVANT were headache (4.5%) and flatulence (3.4%). A lower percentage of the 356 MEZAVANT patients discontinued therapy due to adverse events compared to placebo (2.2% vs. 7.3%). The most frequent adverse event leading to discontinuation from MEZAVANT therapy was exacerbation of ulcerative colitis (0.8%).

The majority of adverse events these trials were mild or moderate in severity. The percentage of patients with severe adverse events was higher in the placebo treatment group (6.1% in placebo, 1.1%

in MEZAVANT 2.4 g/day, 2.2% in MEZAVANT 4.8 g/day). The most common severe adverse events were gastrointestinal disorders which were mainly symptoms associated with ulcerative colitis. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with MEZAVANT in patients experiencing this event.

Overall, the percentage of patients who experienced any adverse event was similar across treatment groups. Treatment related adverse events occurring in MEZAVANT or placebo groups at a frequency of at least 1% in these two trials are listed in Table 2.

Table 2: Treatment-Related Adverse Events in two Phase 3 Trials Experienced by at least 1% of the MEZAVANT Group and at a Rate Greater than Placebo

Event[b]	**MEZAVANT**[a] **2.4 g/day n=177 (%)**	**MEZAVANT**[a] **4.8 g/day n=179 (%)**	**Placebo**[a] **n=179 (%)**
Gastrointestinal Disorders			
Flatulence	3%	3%	2%
Investigations			
Increased alanine aminotransferase	1%	1%	0%
Nervous System Disorders			
Headache	3%	2%	0%
Skin and Subcutaneous Tissue Disorders			
Pruritus	1%	1%	0%
Alopecia	0%	1%	0%

[a] Percentages are based on the number of patients in the safety population for each treatment group.
[b] Treatment-related adverse events for which the placebo rate equals or exceeds the rate for MEZAVANT are abdominal pain, decreased weight (placebo only), dizziness, dyspepsia, nausea, and ulcerative colitis.

Pooled Safety Analysis

The pooled safety analysis of patients with ulcerative colitis who received at least one dose of study medication and participated in clinical studies (short- and long-term, n=1368). Subjects from studies SPD476-301 and SPD476-302 were eligible for enrolment into the longterm extension (ie 12-14 months) safety and tolerability study SPD476-303, which consists of an 8-week acute phase using SPD476 4.8g/day BID and a randomised maintenance phase, to provide long-term safety data on SPD476 2.4g/day QD vs 2.4g/day BID. The majority of subjects did not experience treatment emergent adverse events associated with MEZAVANT. Of the events reported, the majority were mild or moderate in severity. The most frequently reported adverse drug reactions within the pooled safety analysis of the ulcerative colitis patient clinical studies were colitis, headache, abdominal pain, liver function test abnormal, diarrhea and nausea. Adverse drug reactions observed during clinical trials (pooled safety analysis) are listed in Table 3.

Table 3: **Adverse Drug Reactions Associated with MEZAVANT from Pooled Safety Analysis**

Event	**Frequency (%)**
Blood and Lymphatic System Disorders Thrombocytopenia	Uncommon (≥0.1% and <1%)

Event	Frequency (%)
Cardiac Disorders Tachycardia	Uncommon (≥0.1% and <1%)
Ear and Labyrinth Disorders Ear pain	Uncommon (≥0.1% and <1%)
Gastrointestinal Disorders Abdominal distension Abdominal pain Ulcerative Colitis Diarrhea Dyspepsia Flatulence Nausea Vomiting	Common (≥1% and <10%)
Pancreatitis, Rectal polyp	Uncommon (≥0.1% and <1%)
General Disorders and Administration Site Conditions Asthenia Fatigue Pyrexia	Common (≥1% and <10%)
Hepatobiliary Disorders Liver Function Test abnormal (e.g. ALT, AST, Bilirubin)	Common (≥1% and <10%)
Immune System Disorders Hypersensitivity (including rash, pruritis, urticaria and face edema)	Common (≥1% and <10%)
Musculoskeletal and Connective Tissue Disorders Arthralgia Back pain	Common (≥1% and <10%)
Nervous System Disorders Headache	Common (≥1% and <10%)
Dizziness Somnolence Tremor	Uncommon (≥0.1% and <1%)
Respiratory, Thoracic and Mediastinal Disorders Laryngeal pain	Uncommon (≥0.1% and <1%)
Skin and Subcutaneous Tissue Disorders Acne Alopecia	Uncommon (≥0.1% and <1%)
Vascular Disorders Hypertension	Common (≥1% and <10%)
Hypotension	Uncommon (≥0.1% and <1%)

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment-related adverse events, presented by body system, were reported infrequently (less than 1%) by MEZAVANT-treated ulcerative colitis patients in controlled trials (Study SPD476-301 and SPD476-302).

Blood and lymphatic system disorders: thrombocytopenia
Cardiac Disorders: Tachycardia
Ear and Labyrinth Disorders: Ear pain
Gastrointestinal Disorders: Abdominal distension, diarrhea, pancreatitis, rectal polyp, vomiting
General Disorders and Administration Site Conditions: Asthenia, face edema, fatigue, pyrexia
Investigations: Elevated total bilirubin
Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain
Nervous System Disorders: Somnolence, tremor
Respiratory, Thoracic and Mediastinal Disorders: Laryngeal pain
Skin and Subcutaneous Tissue Disorders: Acne, rash, urticaria
Vascular Disorders: Hypertension, hypotension.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In the pivotal studies conducted, there has been no notable change from baseline in mean hematology and biochemistry parameters.

8.5 Post-Market Adverse Reactions

The following Post-Market Adverse Reactions have been seen with MEZAVANT and other mesalamine products.

Blood and Lymphatic System Disorders: Agranulocytosis, aplastic anemia, leucopenia, neutropenia, pancytopenia.
Cardiac Disorders: Myocarditis, pericarditis.
Congenital, Familial and Genetic disorders:, congenital nephrotic syndrome, ectrodactyly
General Disorders and Administration Site Conditions: Chest pain and discomfort.
Hepatobiliary Disorders: Cholelithiasis, hepatitis, hepatotoxicity.
Immune System Disorder: Anaphylactic reaction, angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).
Musculoskeletal and Connective Tissue Disorders: Lupus-like syndrome, myalgia.
Nervous System Disorders: Intracranial pressure increased (see below), neuropathy peripheral.
Pregnancy and Puerperium and Perinatal Conditions: premature labor, foetal anemia, hydrops foetalis, oligohydramnios, fetal tachycardia.
Renal and Urinary Disorders: Chromaturia (see below), nephrogenic diabetes insipidus (see below), nephrotic syndrome, nephrolithiasis, renal failure, tubulointerstitial nephritis.
Reproductive System and Breast Disorders: Oligospermia (reversible).

Respiratory, Thoracic and Mediastinal Disorders: Acute interstitial pneumonitis, allergic asthma hypersensitivity pneumonitis, bronchospasm, eosinophilic pneumonia, interstitial lung disease, pleurisy.
Skin and Subcutaneous Tissue Disorders: Photosensitivity

Descriptions of Selected Adverse Reactions

Chromaturia: Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Intracranial pressure increased: Cases of increased intracranial pressure with papilloedema (pseudotumor cerebri or benign intracranial hypertension) have been reported with mesalamine use. If undetected, this condition can result in constriction of the visual field and permanent vision loss. Mesalamine should be discontinued in patients exhibiting signs and/or symptoms of increased intracranial pressure (headache which may originate behind the eyes and worsen with eye movement, blurred or dimmed vision, double vision, seeing light flashes, difficulty seeing to the side, brief or permanent vision loss).

Nephrogenic diabetes insipidus: Cases of nephrogenic diabetes insipidus have been reported with mesalamine use. The main symptoms of nephrogenic diabetes insipidus are polyuria (excessive urine production/excretion), nocturia (nocturnal polyuria), and polydipsia (excessive thirst). Other symptoms can include tiredness, loss of appetite and weight loss.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No investigations of interaction between MEZAVANT and other drugs except for four commonly used antibiotics have been performed. The studies demonstrated there were no clinically significant interactions of MEZAVANT with these antibiotics (see 9.4 Drug-Drug Interactions).

Drug interactions with nephrotoxic agents, including non-steroidal anti-inflammatory drugs and azathioprine or 6-mercaptopurine have been reported for products containing mesalamine. The reported interactions indicated the concurrent use of mesalamine can increase the potential for blood disorders (especially leucopenia), bone marrow failure, associated complications, and may increase the risk of renal reactions with the respective concurrent drugs (see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Drug-drug interaction studies in healthy adult subjects have been conducted to investigate any effect of MEZAVANT on the pharmacokinetics and safety of four commonly used antibiotics. There were no clinically significant interactions of MEZAVANT with amoxicillin, ciprofloxacin XR, metronidazole or sulfamethoxazole.

The drugs listed in Table 4 have been reported for products containing mesalamine.

Table 4 – Established or Potential Drug – Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Azathioprine, NSAIDs	CS	may increase the risk of renal reactions	Caution is warranted. It is recommended that renal function be evaluated prior to initiation of therapy and periodically while on treatment
Azathioprine	CS	can increase the potential for blood disorders (especially leucopenia), bone marrow failure, and associated complications	Caution is warranted. It is recommended to monitor blood tests, including complete blood cell counts and platelet counts
6-mercaptopurine	CS	can increase the potential for blood disorders (especially leucopenia), bone marrow failure, and associated complications	Caution is warranted. It is recommended to monitor blood tests, including complete blood cell counts and platelet counts

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Administration of a single dose of MEZAVANT 4.8 g with a high fat meal[1] in healthy volunteers resulted in further delay in absorption and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, high fat meal increased systemic exposure of mesalamine (mean C_{max}: ↑91%; mean AUC: ↑16%) compared to results in the fasted state; consideration should be given to this observation when prescribing to patients expected to consume high fat meals. However, MEZAVANT was administered with food, part of an unrestricted diet, in the pivotal Phase 3 trials.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

[1] The high-fat meal, or equivalent, was two eggs fried in butter, two strips of bacon, two slices of toast with butter, 113 g (4 ounces) of hash brown potatoes and 237 mL (8 ounces) of whole milk.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of mesalamine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelial cells.

Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

In non-clinical studies, mesalamine has been shown to possess anti-oxidant properties in a range of systems in vitro. It also stimulates phospholipase D activity which may inhibit pro-inflammatory events. Mesalamine has also been shown to inhibit the production of the metabolites of arachidonic acid, particularly leukotriene B4 (LTB4), an important mediator in chronic inflammatory diseases.

Mesalamine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key pro inflammatory cytokines. More recently, it has been proposed that impairment of PPAR-γ nuclear receptors (γ-form of peroxisome proliferator activated receptors) may be implicated in ulcerative colitis. PPAR-γ receptor agonists have shown efficacy in ulcerative colitis and evidence has been accumulating that the mechanism of action of mesalamine may be mediated by PPAR-γ receptors.

10.2 Pharmacodynamics

The pharmacodynamic actions of mesalamine occur in the colonic/rectal mucosa local to the delivery of drug from MEZAVANT into the lumen. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalamine is inversely correlated with mucosal concentrations of mesalamine. However, plasma concentrations representing systemically absorbed mesalamine are not believed to contribute extensively to efficacy.

10.3 Pharmacokinetics

Table 5: **Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of MEZAVANT under Fasting Conditions**

Parameter[1] of Mesalamine	MEZAVANT 1.2 g n=47	MEZAVANT 2.4 g n=48	MEZAVANT 4.8 g n=48
AUC_{0-t} (ng.h/mL)	9039[+] (5054)	20538 (12980)	41434 (26640)
$AUC_{0-\infty}$ (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_{lag}* (h)	2.0** (0-8.0)	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)

[1] Arithmetic mean of parameter values are presented except for T_{max} and T_{lag}
* Median (min, max); [+]n=43, [•]n=27, [§]n=33, [#]n=36, **n=46

The pharmacokinetic information in this section is based on data from Phase 1 studies with MEZAVANT and from studies carried out with other formulations of mesalamine.

MEZAVANT contains a 1.2 g core of mesalamine formulated in a multi-matrix system. This system is coated with methacrylic acid – methyl methacrylate copolymer (1:1) and methacrylic acid – methyl methacrylate copolymer (1:2), which are designed to dissolve at pH 7 and above, facilitating the extended delivery of effective concentrations of mesalamine through the entire colon with limited systemic absorption.

Absorption

The total absorption of mesalamine from MEZAVANT 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose. Steady-state was achieved generally by 2 days after dosing.

Gamma-scintigraphy studies have shown that a single dose of MEZAVANT 1.2 g (one tablet) passed rapidly and intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radiolabelled tracer throughout the colon and rectum, indicating that mesalamine had distributed throughout the targeted site of action. Complete disintegration of MEZAVANT and complete release of mesalamine occurred after approximately 17.4 hours. Availability of mesalamine in the colon begins at 6 hours after dosing and continues beyond 24 hours post-dose. Following a single dose of MEZAVANT 4.8 g, detectable levels of mesalamine remain in the plasma for up to 72 hours post dose.

In a single- and multiple dose pharmacokinetic study, MEZAVANT 2.4 or 4.8 g was administered once daily with standard meals in 56 healthy volunteers (28 per dose group). Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Accumulation was found to be between 1.7- and 2.4-fold and was independent of dose. This extent of accumulation was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

After a single dose of MEZAVANT, total systemic exposure of 5-ASA appeared to increase slightly more than dose proportionately, with area under the plasma concentration-time curve (AUC) increasing approximately 2.5-fold for a 2-fold dose increase from 2.4 g to 4.8 g. However there was no evidence of

steady-state systemic exposure increasing more than proportionately with dose.

In a single dose study, MEZAVANT 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 9-12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (see Table 5). 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 MEZAVANT. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionately between 1.2 g and 2.4 g and sub-proportionately between 2.4 g and 4.8 g MEZAVANT, with the dose-normalized value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means.

Administration of a single dose of MEZAVANT 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}: ↑91%; mean AUC: ↑16%) compared to results in the fasted state.

In a single-dose pharmacokinetic study of MEZAVANT, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers [28 young (18-35 years); 28 elderly (65-75 years); 15 elderly (>75 years)]. Increased age resulted in increased systemic exposure (up to approximately 2-fold, based on AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) to mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, but did not affect the percentage of mesalamine absorbed (see Table 6). Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Table 6: **Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of MEZAVANT 4.8 g Fasting Conditions to Young and Elderly Subjects**

Parameter of 5-ASA	Young Subjects (18-35 yrs) n=28	Elderly Subjects (65-75 yrs) n=28	Elderly Subjects (>75 yrs) n=15
AUC_{0-t} (ng.h/mL)	51570 (23870)	73001 (42608)	65820 (25283)
$AUC_{0-\infty}$ (ng.h/mL)	58057[b] (22429)	89612[c] (40596)	63067[d] (22531)
C_{max} (ng/mL)	2243 (1410)	4999 (4381)	4832 (4383)
t_{max}[a] (h)	22.0 (5.98 – 48.0)	12.5 (4.00 – 36.0)	16.0 (4.00 – 26.0)
t_{lag}[a] (h)	2.00 (1.00 – 6.00)	2.00 (1.00 – 4.00)	2.00 (2.00 – 4.00)
$t_{½}$ (h), terminal phase	5.68[b] (2.83)	9.68[c] (7.47)	8.67[d] (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
[a] Median (min max), [b]n=15, [c]n=16, [d]n=13

Distribution

Following dosing of MEZAVANT, the distribution profile of mesalamine is presumed to be the same as that for other mesalamine containing products. Mesalamine has a relatively small volume of distribution of approximately 18 L, confirming minimal extravascular penetration of systemically-

available drug, which is consistent with the absence of any significant secondary pharmacology. Mesalamine is 43% bound to plasma proteins when in vitro plasma concentrations are 2.5 mcg/mL.

Metabolism

The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid, which is pharmacologically inactive. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and in the cytosol of intestinal mucosal cells, principally by NAT-1. Although this enzyme is known to be subject to genetic polymorphism, NAT-1 genotypes have been shown not to be predictive of mesalamine efficacy or toxicity.

Elimination

Elimination 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 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine at steady-state, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half lives for mesalamine and its major metabolite after administration of MEZAVANT 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.

Special Populations and Conditions

- **Pediatrics:** No information is available in patients who are less than 18 years of age (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).
- **Geriatrics:** Systemic exposure to mesalamine increased by up to approximately 2-fold in elderly subjects (>65 years) compared with younger adult subjects (18-35 years) after a 4.8 g single dose of MEZAVANT (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance. The potential impact on the safe use of MEZAVANT in the elderly population in clinical practice should be considered (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).
- **Sex:** No consistent trend effect was observed in the clinical trials based on sex.
- **Genetic Polymorphism:** Mesalamine is principally metabolised by NAT-1. Although this enzyme is known to be subject to genetic polymorphism, NAT-1 genotypes have been shown not to be predictive of mesalamine efficacy or toxicity.
- **Ethnic Origin:** No pharmacokinetic information is available that examines MEZAVANT in different ethnic origins.
- **Hepatic Insufficiency:** No pharmacokinetic information is available for patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 8 ADVERSE REACTIONS).
- **Renal Insufficiency:** No pharmacokinetic information is available for patients with mild, moderate and severe renal impairment (see 7 WARNINGS AND PRECAUTIONS, Renal; 8 ADVERSE REACTIONS).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 25°C; excursions permitted to 30°C.

Keep out of reach and sight of children

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

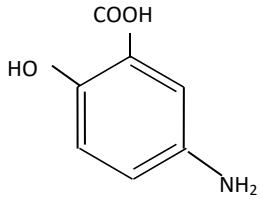
Drug Substance

Proper name: mesalamine

Chemical name: 5-amino-2-hydroxybenzoic acid

Molecular formula and molecular mass: $C_7H_7NO_3$ 153.14

Structural formula:



Physicochemical properties:

Mesalamine is an almost white to light pink/gray/brown powder or crystals that decomposes at 280°C and is very slightly soluble in water.

The pH of 2.5% aqueous suspension is 3.5 - 4.5.

pKa value: 5.8

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Active, Mild to Moderate Ulcerative Colitis:

Two similarly designed, randomized, double-blind, placebo-controlled trials were conducted in adult patients with active, mild to moderate ulcerative colitis. Study SPD476-301 assessed the efficacy and safety of MEZAVANT 2.4 g/day (1.2 g given twice daily) and 4.8 g/day (given once daily) against placebo in 280 patients. Study SPD476-302 assessed the safety and efficacy of MEZAVANT 2.4 g/day and 4.8 g/day (both given once daily) against placebo in 341 patients. A pH dependent delayed-release mesalamine 2.4 g/day (administered as two 400 mg tablets given three times daily) was included in this study as a reference arm; the study was not designed to demonstrate non-inferiority of MEZAVANT against pH dependent delayed release mesalamine.

Maintenance of remission:

A multicenter, randomized, double-blind, double-dummy, parallel-group, non-inferiority, active comparator study (SPD476-304) was designed to assess the number of subjects who remained in endoscopic remission (maintenance of mucosal healing) following 6 months of study treatment. Subjects were randomized in a 1:1 ratio to receive either MEZAVANT 2.4 g/day administered once daily (QD) or pH-dependent delayed-release mesalamine 1.6 g/day administered as two 400 mg tablets given twice daily (BID).

Table 7: Summary of Baseline Demographic Characteristics for Patients with Ulcerative Colitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
SPD476-301	Randomized, double-blind, placebo-controlled trial conducted in subjects with active, mild to moderate UC to assess the efficacy and safety of MEZAVANT.	2.4 g/day administered as 1.2 g twice daily and 4.8 g/day administered once daily Oral 8 weeks	262[a]	41.5 (18-76)	M=51.5% F=48.5%
SPD476-302	Randomized, double-blind, placebo-controlled trial conducted in subjects with active, mild to moderate UC to assess the safety and efficacy of MEZAVANT. This study included a comparator, pH-dependent delayed release mesalamine, as an internal reference arm.	2.4 g/day and 4.8 g/day administered once daily pH-dependent delayed-release mesalamine 2.4 g/day, administered as 2x400 mg three times daily	341[a]	43.2 (18-78)	M=47.5% F=52.5%
SPD476-304	Randomized, double-blind, double-dummy, parallel-group, non-inferiority, active comparator study conducted in subjects with mild to moderate UC to assess the number of subjects who remained in endoscopic remission following six (6) months of study treatment.	2.4 g/day administered once daily pH-dependent delayed-release mesalamine 1.6 g/day in divided dose, administered as 0.8 g twice daily (BID)	679[b]	45.4 (18-85)	M=50.8% F=49.2%

[a] Based on ITT population

[b] Based on Per Protocol population

14.2 Study Results

Induction of Remission, Including Clinical Remission and Mucosal Healing

The primary efficacy endpoint in studies SPD476-301 and SPD476-302 was to compare the percentage of patients in remission, a composite endpoint indicative of clinical remission and mucosal healing, after 8 weeks of treatment for the MEZAVANT treatment groups vs. placebo. Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) score of ≤1. To be considered in remission, a subject was required to have no blood in stools and normal stool frequency. Also, they could have either a Physician Global Assessment of 1 (mild disease) or improvement of the mucosal appearance

that lead to a maximum sigmoidoscopy score of 1 (mild erythema, decreased vascularity, minimal granularity) as long as there had been at least a 1-point drop from baseline in the sigmoidoscopy score. The scoring system used for sigmoidoscopy was modified to be more stringent than the standard UC-DAI system, which allows patients with mild friability to be given a sigmoidoscopy score of 1. Results for the primary variable of remission in study SPD476-301 are shown in Table 8. Both MEZAVANT 2.4 g/day (1.2 g given twice daily) and 4.8 g/day (given once daily) demonstrated superiority over placebo. Results for study SPD476-302 are also shown in Table 8. Both MEZAVANT 2.4 g/day and 4.8 g/day (both given once daily) demonstrated superiority over placebo.

Table 8: Summary of Primary Efficacy Results for Studies SPD476-301 and SPD476-302 in Mild to Moderate, Active Ulcerative Colitis – ITT Population

	SPD476-301			SPD476-302			
	Placebo n=85	MEZAVANT 2.4 g/day BID n=88	MEZAVANT 4.8 g/day QD n=89	Placebo n=86	MEZAVANT 2.4 g/day QD n=84	MEZAVANT 4.8 g/day QD n=85	pH-dependent delayed-release mesalamine[a] 2.4 g/day (0.8 g given TID) n=86
Number of subjects in remission*							
n	11	30	26	19	34	35	28
(%)	(12.9)	(34.1)	(29.2)	(22.1)	(40.5)	(41.2)	(32.6)
Comparison of active vs. placebo[‡]							
Odds ratio		3.48	2.78		2.40	2.47	1.70
CI		1.44, 8.41	1.27, 6.06		1.23, 4.69	1.15, 5.30	0.86, 3.36
p-value[†]		0.001	0.009		0.010	0.007	0.124

[a] pH-dependent delayed-release mesalamine was included in this study as a reference arm; the study was not designed to demonstrate non-inferiority of MEZAVANT against pH-dependent delayed-release mesalamine.

* Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) score of ≤1. To be considered in remission, a subject was required to have no blood in stools and normal stool frequency. Also, they could have either a Physician Global Assessment of 1 (mild disease) or improvement of the mucosal appearance that lead to a maximum sigmoidoscopy score of 1 (mild erythema, decreased vascularity, minimal granularity) as long as there had been at least a 1-point drop from baseline in the sigmoidoscopy score. The scoring system used for sigmoidoscopy was modified to be more stringent than the standard UC-DAI system, which allows patients with mild friability to be given a sigmoidoscopy score of 1.

[‡] Values from the chi-squared test.

[†] Study-wise false-positive error rate was controlled using the Bonferroni-Holm method. The treatment comparison with the smaller p-value was evaluated at the 0.025 significance level. If this was significant, the treatment comparison with the larger p-value was evaluated at the 0.05 significance level. Confidence Intervals (CI) presented are analogous to the significance level, i.e., 97.5% and 95%.

The studies were not powered to look at differences between MEZAVANT doses. There was no statistically significant difference in remission rates between MEZAVANT 2.4 g/day twice daily and MEZAVANT 4.8 g/day once daily or between MEZAVANT 2.4 g/day once daily and MEZAVANT 4.8 g/day once daily. The secondary efficacy parameters, including clinical improvement and change in UC-DAI score and its components (including assessment of treatment failure, clinical remission and sigmoidoscopy) supported the primary findings by demonstrating statistical significance over placebo (results are shown in Table 9 and Table 10). There was no statistically significant difference between

MEZAVANT 2.4 g/day and 4.8 g/day dose groups in clinical improvement, clinical remission and sigmoidoscopic improvement; however, MEZAVANT 4.8 g/day showed trends for improved efficacy over MEZAVANT 2.4 g/day after 8 weeks of treatment in terms of sigmoidoscopic outcome (one of four components of the UC DAI) and clinical improvement (defined as a drop in the UC-DAI score of at least 3 points).

Table 9: Study SPD476-301: Secondary Efficacy Results (% Patients)

Secondary Efficacy Endpoints	**MEZAVANT 2.4 g/day (Given 1.2g BID) n=88**	**MEZAVANT 4.8 g/day (Given QD) n=89**	**Placebo n=85**
Clinical Improvement[a] *(reduction in UC-DAI score from baseline of ≥3 points)*	55.7%***	59.6%***	25.9%
Treatment Failure[a] *(unchanged, worsened, or missing UC-DAI scores)*	28.4%***	24.7%***	54.1%
Clinical Remission[a] *(scores of 0 for stool frequency and rectal bleeding)*	37.5%**	32.6%*	18.8%
Sigmoidoscopic Improvement[a]	64.8%**	71.9%***	36.5%
Change from baseline in UC-DAI score *(least squares mean change)*	-2.71***	-3.46***	-0.79

[a] the % data represents the proportion of subjects.

* p<0.05, **p<0.01, ***p<0.001 (each vs. placebo)

Clinical Improvement, Treatment Failure and Clinical Remission: p-value from the chi-squared test.

Sigmoidoscopic Improvement: p-value from the Mantel-Haenszel chi-squared test with the alternative hypothesis of linear association.

Change from baseline in UC-DAI score: ANCOVA with change from baseline as the response variable and baseline UC-DAI score, treatment group and pooled centre as explanatory variables.

Table 10: Study SPD476-302: Secondary Efficacy Results (% Patients)

Secondary Efficacy Endpoints	**MEZAVANT 2.4 g/day (Given QD) n=84**	**MEZAVANT 4.8 g/day (Given QD) n=85**	**pH-dependent delayed-release mesalamine**[a] **2.4 g/day (0.8 g given TID) n=86**	**Placebo n=86**
Clinical Improvement[b] *(reduction in UC-DAI score from baseline of ≥3 points)*	60.7%**	64.7%***	55.8%*	39.5%
Treatment Failure[b] *(unchanged, worsened, or missing UC-DAI scores)*	21.4%***	20.0%***	27.9%**	47.7%
Clinical Remission[b] *(scores of 0 for stool frequency*	41.7%**	41.2%**	33.7%NS	22.1%

Secondary Efficacy Endpoints	MEZAVANT 2.4 g/day (Given QD) n=84	MEZAVANT 4.8 g/day (Given QD) n=85	pH-dependent delayed-release mesalamine[a] 2.4 g/day (0.8 g given TID) n=86	Placebo n=86
and rectal bleeding)				
Sigmoidoscopic Improvement[b]	70.2%***	76.5%***	60.5%*	41.9%
Change from baseline in UC-DAI score *(least squares mean change)*	-3.34**	-3.58**	-3.11*	-1.94

[a] pH-dependent delayed-release mesalamine was included in this study as a reference arm and was not designed to demonstrate non-inferiority of MEZAVANT against pH-dependent delayed-release mesalamine.

[b] the % data represents the proportion of subjects.

*p<0.05, **p<0.01, ***p<0.001 (each vs. placebo); NS: p>0.05 (vs. placebo)

Clinical Improvement, Treatment Failure and Clinical Remission: p-value from the chi-squared test.

Sigmoidoscopic Improvement: p-value from the Mantel-Haenszel chi-squared test with the alternative hypothesis of linear association.

Change from baseline in UC-DAI score: ANCOVA with change from baseline as the response variable and baseline UC-DAI score, treatment group and pooled centre as explanatory variables.

Maintenance of remission, including clinical remission and mucosal healing

The primary efficacy endpoint in study SPD476-304 was the proportion of subjects in endoscopic remission at Month 6 using the Per Protocol population. Endoscopic remission (mucosal healing) was defined by a modified UC-DAI endoscopy component score of ≤1. MEZAVANT met the primary endpoint of non-inferiority of -10% versus pH-dependent delayed release mesalamine in the proportion of subjects in endoscopic remission (maintenance of mucosal healing) at 6 months.

Table 11: Summary of Primary Efficacy Results for Study SPD476-304 in Mild to Moderate Ulcerative Colitis

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6 (Mucosal Healing) (Per Protocol Population)		
		MEZAVANT 2.4 g/day (given QD) n=343
Month 6	Subjects in endoscopic remission* (n, %)	287 (83.7)

* Endoscopic remission (mucosal healing) was defined by a modified UC-DAI endoscopy component score of ≤1. The scoring system used for sigmoidoscopy was modified to be more stringent than the standard UC-DAI system, which allows patients with mild friability to be given a sigmoidoscopy score of 1.

The proportion of subjects who reached remission in this study using MEZAVANT 2.4 g/day QD (83.7%) was similar to that seen using the comparator (pH-dependent delayed-release mesalamine 1.6 g/day [0.8 g BID]; 81.5%).

Secondary endpoint analyses demonstrated that MEZAVANT achieved a similarly high proportion of subjects in endoscopic remission (mucosal healing) with no or mild symptoms, clinical remission, improved or same endoscopy scores, and improved or same Physician Global Assessment scores, as compared to pH-dependent delayed-release mesalamine as well as similar changes in modified UC-DAI scores.

A randomized, open-label extension study to studies SPD476-301 and SPD476-302 was designed to assess the long-term safety and tolerability of MEZAVANT 2.4 g/day administered once daily and in 2 divided doses (1.2 g BID) in the maintenance of ulcerative colitis in remission over 12 months. This study, study SPD476-303, included an 8-week Acute Extension Phase during which MEZAVANT 4.8 g/day dose was administered BID, and a 12-month Maintenance Phase during which MEZAVANT 2.4 g/day dose was administered either (1.2 g) BID or QD. Efficacy was a secondary objective of this extension study.

The 12-month safety results from the SPD476-303 study are consistent with previously reported safety data. The efficacy endpoints were time to relapse for the Maintenance Phase; and the percentage of subjects in remission at the end of the study for the Acute and Maintenance phases.

Time to relapse was defined as the time at which a subject withdrew from the Maintenance Phase due to a requirement for alternative ulcerative colitis medication denoted by “Lack of Efficacy/Relapse.” The proportion of subjects withdrawing due to a need for alternative ulcerative colitis medication in the Maintenance Phase Efficacy population was low. Both treatment groups had similar times to relapse for the duration of the Maintenance Phase. At 12 months (360 days), the proportion of subjects who had not relapsed (i.e., relapse free) was approximately 88% in the MEZAVANT 2.4 g/day QD group and 92% in the MEZAVANT 1.2 g BID (total 2.4 g/day) group.

Remission was defined as modified UC-DAI score ≤1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from parent study baseline in the sigmoidoscopy score. Overall 59.5% of subjects achieved remission at the end of the Acute Extension Phase (Month 2). At Month 12 of the Maintenance Phase, 64.4% of subjects in the MEZAVANT 2.4 g/day QD group and 68.5% of subjects in the MEZAVANT 1.2 g BID (total 2.4 g/day) group met the strict remission criteria; no statistically significant differences were observed between treatment groups.

An open-label study (SPD476-404) was designed to assess clinical recurrence related to compliance with treatment with MEZAVANT 2.4 g/day given once daily for the maintenance of quiescent ulcerative colitis. Subjects entered the 12-month Maintenance Phase either directly or after completion of an 8-week acute phase. The primary analysis was the proportion of subjects with clinical recurrence at Month 6 of the Maintenance Phase. 76.5% of subjects who had sufficient data to calculate clinical recurrence at Month 6 did not have disease recurrence after 6 months of maintenance treatment with MEZAVANT.

The results of the secondary efficacy parameters (clinical recurrence at 12 months, proportion of subjects with quiescent ulcerative colitis, endoscopic remission, and time to clinical recurrence) supported the primary findings of consistently maintaining quiescence of ulcerative colitis through 12 months of maintenance treatment with MEZAVANT. Another study objective was also to assess health-related quality of life (QoL) at baseline of the Acute Phase, Week 8 Acute Phase/Baseline Maintenance Phase, 6 months, and 12 months. Non quiescent UC subjects who received MEZAVANT treatment during the Acute Phase showed statistically and clinically significant improvement on almost all measured aspects of health related QoL measures using the three questionnaires (Medical Outcomes Study 12 Item Short Form Health Survey, the Short Inflammatory Bowel Disease Questionnaire, and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem v2.0), particularly

on physical role, disease-related QoL (such as pain, urgency, and anxiety), and work productivity loss and activity impairment.

Pharmacokinetics

In a parallel-group, two-period pharmacokinetic study of MEZAVANT 2.4 g/day or 4.8 g/day, where single and multiple doses were administered once daily with standard meals in 56 healthy volunteers (28 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. Accumulation was found to be between 1.7- and 2.4-fold and was independent of dose. This extent of accumulation was only modestly greater (1.1- to 1.4-fold) than predictable from single-dose pharmacokinetics. There was no evidence of steady-state systemic exposure increasing more than proportionately with dose. The principal pharmacokinetic parameters are presented in Table 12.

Table 12: **Principal Pharmacokinetic Parameters of 5-ASA following Administration of MEZAVANT in a 2.4 g/day and 4.8 g/day Single and Multiple Dose Study**

Study/Dose	2.4 g single dose n=28	2.4 g/day QD multiple dose (Day 14 data) n=28	4.8 g single dose n=28	4.8 g/day QD multiple dose (Day 14 data) n=28
Parameter				
AUC_T (ng.h/mL) (mean±SD	18573 ± 10969 (t=up to 120h)	22319 ± 13697 (t=24h)	47785 ± 22421 (t=up to 120h)	49559 ± 23780 (t=24h)
AUC_I ng.h/mL) (mean±SD**)**	19852 ± 11740	N/A	48141 ± 25627	N/A
C_{MAX} (ng/mL) (mean±SD)	2932 ± 2957	2918 ± 2164	4385 ± 3033	5280 ± 3146
T_{MAX}(h) (mean±SD	13.2 ± 10.0	9.07 ± 5.37	14.4 ± 9.68	9.60 ± 3.78
$T_{½}$ (h) (mean±SD)	7.41 ± 4.65	N/A	6.28 ± 5.31	N/A
t_{lag} (h) (mean±SD)	5.2 ± 3.9	0.0 ± 0.0	4.9 ± 4.2	0.21 ± 0.83
% Dose absorbed	25.2 ± 10.4	22.4 ± 9.25	27.0 ± 12.6	20.8 ± 11.6

N/A: Not Applicable

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: 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. This dose is 2.2 times the maximum recommended human dose (based on body surface area comparison) of MEZAVANT. 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 body surface area comparison) of MEZAVANT.

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

Reproductive and Developmental Toxicology: No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 296 mg/kg/day.

Reproduction studies have been performed in rats at doses up to 480 mg/kg/day and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. Animal reproduction studies are not always predictive of human response.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MEZAVANT®

mesalamine Delayed- and Extended-Release Tablets

Read this carefully before you start taking **MEZAVANT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MEZAVANT**.

What is MEZAVANT used for?

- To treat symptoms related to ulcerative colitis in adults. Ulcerative colitis is a condition where the large bowel (colon) and back passage (rectum) becomes red and swollen (inflamed).
- To help prevent the recurrence of ulcerative colitis in adults.

MEZAVANT is not for use in children under the age of 18.

How does MEZAVANT work?

MEZAVANT is an anti-inflammatory drug. MEZAVANT is believed to stop the production of certain substances in your body that cause swelling (inflammation). MEZAVANT tablets use a technology called Multi Matrix System®. This system prevents the medicine from being released early. It also allows the medicine to work for an extended period of time throughout the colon and rectum.

What are the ingredients in MEZAVANT?

Medicinal ingredients: **mesalamine**

Non-medicinal ingredients: carnauba wax, magnesium stearate, methacrylic acid – methyl methacrylate copolymer (1:1), methacrylic acid – methyl methacrylate copolymer (1:2), polyethylene glycol (macrogol) 6000, red ferric oxide (E172), silica (colloidal hydrated), sodium carboxymethylcellulose, sodium starch glycolate (type A), stearic acid, talc, titanium dioxide (E171) and triethylcitrate.

MEZAVANT tablets do not contain gluten, lactose or phthalates.

MEZAVANT comes in the following dosage forms:

MEZAVANT 1.2 g delayed- and extended-release tablets.

Do not use MEZAVANT if:

- you are allergic to mesalamine or any of the ingredients in MEZAVANT

- you are allergic to a family of drugs known as salicylates [which includes acetylsalicylic acid (i.e., Aspirin®[2])]
- you have severe liver problems
- you have severe kidney problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MEZAVANT. Talk about any health conditions or problems you may have, including if you:

- have a narrow or blocked upper digestive tube (e.g., pyloric stenosis).
- have any kidney or liver problems.
- have a chronic lung condition (e.g., asthma).
- have ulcers in your stomach or in the first part of the small intestines.
- have a blocked urinary tract.
- had a heart condition that causes inflammation of the heart (which may be the results of an infection of the heart).
- have eczema. A condition that causes dry, itchy rashes on your skin. Your skin may be more sensitive to sunlight when taking MEZAVANT.
- have had previous allergy (hypersensitivity reaction) to sulfasalazine. Sulfasalazine is an ingredient in other medicines used to treat ulcerative colitis.

Other warnings you should know about:

Treatment with MEZAVANT can increase your risk of certain side effects, including:

- **Blood Disorder**: Treatment with MEZAVANT can cause serious blood disorders. The risk of this side effect is increased when you take immunosuppressant drugs that contain 6-mercaptopurine (e.g., Purinethol) or azathioprine (e.g., Imuran). Speak to your doctor immediately if you experience any of the following symptoms:
    - Unexplained bleeding
    - Bruising
    - Fever
    - Sore throat
- **Kidney stones**: You may develop kidney stones when using MEZAVANT. Be sure to drink enough liquids while you are taking MEZAVANT. Speak to your doctor immediately if you experience any of the following symptoms:
    - Blood in urine
    - Urinating more often
    - Pain in your back, stomach, side or groin

Pregnancy and breastfeeding

If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.

- Avoid becoming pregnant while you are taking MEZAVANT. It may harm your unborn baby.

[2] Aspirin is a registered trade-mark of Bayer Aktiengesellschaft

- Tell your doctor right away if you become pregnant or think you may be pregnant during treatment with MEZAVANT.
- Taking MEZAVANT during pregnancy have been reported to cause
    - early labor
    - birth defects in babies. The baby may develop kidney and heart issues.
- You should not breastfeed or plan to breastfeed during treatment. If you breastfeed your baby while taking MEZAVANT your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea. Your doctor may advise you to stop breastfeeding your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MEZAVANT:

- Azathioprine (e.g., Imuran) or 6-mercaptopurine (e.g., Purinethol) or other drugs known to affect your bone marrow. The bone marrow is responsible for creating blood cells. Taking MEZAVANT with these drugs may increase your risk of having a blood disorder, bone marrow problems or other problems.
- Drugs known to affect the kidney. This can include anti-inflammatory drugs (Nonsteroidal anti-inflammatory drugs (NSAIDs)) and azathioprine drugs. Taking MEZAVANT with these drugs may increase your risk of side effects to your kidneys.

Treatment with MEZAVANT can affect the results of a urine test. Tell your doctor or nurse that you are taking MEZAVANT when taking a urine test.

How to take MEZAVANT:

- Take MEZAVANT exactly as your doctor tells you to take it. Do NOT take more of it than prescribed. Speak to your doctor or pharmacist if you are not sure.
- Take MEZAVANT with food. Swallow tablets whole with liquids. Do NOT crush or chew the tablets.

Usual dose:

<u>Adult Dose to treat a sudden onset of ulcerative colitis symptoms</u>
Take two to four 1.2 g tablets (equal to 2.4 g to 4.8 g) once a day.

<u>Maintenance Adult Dose to prevent the recurrence of ulcerative colitis</u>
Take two 1.2 g tablets (equal to 2.4 g) once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much MEZAVANT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your medicine, then take it as usual the next day. Do not take two doses to make up for a forgotten dose.

What are possible side effects from using MEZAVANT?

These are not all the possible side effects you may have when taking MEZAVANT. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of MEZAVANT are:

- Diarrhea
- Headache
- Nausea
- Stomach pain

Other possible side effects of MEZAVANT may include:

- Acne or itchy skin
- Digestive tract problems
  - gas
  - upset or bloated stomach
  - vomiting
- Dizziness
- Ear or throat pain
- Feeling weak, sleepy or tired
- Fever
- Hair loss
- Muscle, joint and back pain
- Skin is sensitive to sunlight
- Trembling or shaking
- Urine discolouration (urine may become discolored reddish-brown when MEZAVANT comes in contact with sodium hypochlorite, bleach in the toilet water)

Your doctor may run tests, including a blood test, to check your liver function and blood cell counts.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON **Allergic reaction:** hives, rash, swollen face			√

Serious side effects and what to do about them			
	Talk to your healthcare professional		
Symptom / effect	**Only if severe**	**In all cases**	**Stop taking drug and get immediate medical help**
Unknown **Other allergic reaction**: swelling of the mouth, throat, difficulty in breathing and worsening asthma			√
Colitis (inflamed colon): diarrhea, blood in stool, abdominal pain, cramping, nausea and vomiting, fever			√
High blood pressure: shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
COMMON **Acute Intolerance Syndrome**: cramping, acute stomach pain, bloody and excessive stools (diarrhea), fever, headache and rash. These symptoms could be a sign of a serious condition which occurs rarely but means your treatment would have to be stopped immediately		√	
UNCOMMON **Blood problems:** unexplained bruising, unusual bleeding (for example, nose bleeds), fever, sore throat		√	
Worsening of Ulcerative Colitis (inflamed rectum and colon): severe or persistent		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
diarrhea, abdominal pain, nausea and vomiting, fever			
Pancreatitis (inflamed or swollen pancreas): abdominal pain and feeling sick		√	
Tachycardia (abnormal heartbeat): dizziness, light headedness, shortness of breath, racing heart		√	
Rectal polyp (a non-cancerous growth in the back passage): constipation and bleeding		√	
Low blood pressure: dizziness, light headedness, fainting		√	
RARE **Kidney problems** (such as inflammation and scarring of the kidney or kidney failure): blood in the urine, fever, increased or decreased urine output, mental status changes (drowsiness, confusion, coma), nausea, vomiting, rash, swelling of the body, weight gain (from retaining fluid)		√	
Kidney stones (hard little pebbles that form in your kidneys): blood in urine, urinating more often, pain in your back, side, belly or groin		√	

Serious side effects and what to do about them			
	Talk to your healthcare professional		
Symptom / effect	**Only if severe**	**In all cases**	**Stop taking drug and get immediate medical help**
UNKNOWN FREQUENCY **Hepatitis** (inflammation of the liver): jaundice (yellowing of the skin and eyes) and flu-like symptoms		√	
Reversible decline in sperm production		√	
Nephrogenic diabetes insipidus (diabetes caused by kidney problems): increased thirst, frequent urination, waking up during the night to urinate, possible bed wetting, tiredness, loss of appetite and weight loss		√	
Lupus-Like Syndrome: butterfly shaped skin rash typically on face, skin sensitive to sunlight, joint pain and/or arthritis		√	
Abnormal or damaged nerves: numbness and tingling sensation		√	
Hepatotoxicity (liver damage): stomach pain, nausea, vomiting, loss of appetite, jaundice (yellow skin or eyes), dark-coloured urine, light-coloured stool		√	

Serious side effects and what to do about them			
	Talk to your healthcare professional		
Symptom / effect	**Only if severe**	**In all cases**	**Stop taking drug and get immediate medical help**
Myocarditis/ Pericarditis (inflammation of the heart muscle and lining around the heart): abnormal heartbeat, chest pain that may resemble a heart attack, fatigue, fever and other signs of infection including headache, muscle aches, sore throat, diarrhea, or rashes, joint pain or swelling, leg swelling, shortness of breath		√	
Pleurisy (inflammation of the sheet like layers that cover the lungs): difficulty in breathing or wheezing, sometimes with chest pain		√	
Hypersensitivity pneumonitis (inflammation of lungs due to an allergic reaction): fever, cough, chills, and shortness of breath			√
Serious Skin Conditions (Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms): swelling of the skin or serious skin rash seen as severe blisters of the skin and mucous membranes			√
Toxic epidermal necrolysis (TEN) (rare and serious skin condition): peeling of the skin, painful raw areas			√

Serious side effects and what to do about them			
	Talk to your healthcare professional		
Symptom / effect	**Only if severe**	**In all cases**	**Stop taking drug and get immediate medical help**
Increased pressure in brain causing headache which may originate behind your eyes and worsen with eye movements, with blurred or dimmed vision, double vision, seeing light flashes, difficulty seeing to the side, and brief or permanent vision loss. These may be associated with dizziness, nausea, vomiting, ringing in ears			√
Infant diarrhea when breastfeeding		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 25°C), excursions permitted to 30°C.

Keep out of the reach and sight of children.

If you want more information about MEZAVANT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.takeda.com/en-ca, or by calling 1-800-268-2772.

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