PRODUCT MONOGRAPH

MEZAVANT®*

mesalamine

1.2g Delayed- and Extended-Release Tablets

Lower Gastrointestinal Anti-Inflammatory

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MEZAVANT®

mesalamine Delayed- and Extended-Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Delayed- and extended-release tablet 1.2g	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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.

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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Results of a single-dose study on the comparative pharmacokinetic profiles in elderly healthy subjects versus young healthy subjects indicate that 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 4.8g single dose of MEZAVANT. 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 **Warnings and Precautions – Special Populations, Geriatrics; Action and Clinical Pharmacology – Pharmacokinetics, Absorption**).

Pediatrics (<18 years of age):
The safety and effectiveness of mesalamine has not been established in children.

CONTRAINDICATIONS

- Patients who are hypersensitive to any salicylates (including mesalamine) or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the Product Monograph.
- Patients with severe renal impairment (GFR <30mL/min/1.73m^2) and/or severe hepatic impairment (see **Warnings and Precautions - Renal** and **Hepatic/Biliary/Pancreatic**).

WARNINGS AND PRECAUTIONS

General

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.

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.

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to MEZAVANT tablets or other compounds that contain or are converted to mesalamine. Therefore, caution should be exercised when treating patients allergic to sulfasalazine due to the potential risk of cross sensitivity reactions between sulfasalazine and mesalamine.

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 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 **Warnings and Precautions – Renal**).

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 **Warnings and Precautions – Hepatic/Biliary/Pancreatic**).

Patients should be instructed to swallow MEZAVANT tablets whole, 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.

Administration of a single dose of MEZAVANT 4.8g with a high-fat meal in healthy volunteers increased systemic exposure of mesalamine compared to results in the fasted state (see **Dosage and Administration**; **Drug Interactions – Drug-Food Interactions**).

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 **General** sub-section above.

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 **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 **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.

Photosensitivity

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

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 **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.

Respiratory

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

Special Populations

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.

Nursing Women:
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. Diarrhea has been reported in breastfed infants of mothers exposed to mesalamine, including one serious case.

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, consider discontinuation of breastfeeding. Caution

should be exercised if MEZAVANT is administered to a nursing mother and used only if the benefits outweigh the risks.

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

Geriatrics (≥65 years of age):
Clinical trials of MEZAVANT did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Results of a single-dose study on the comparative pharmacokinetic profiles in elderly healthy subjects versus young healthy subjects indicate that 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 4.8g single dose of MEZAVANT (see **Action and 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. 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.

ADVERSE REACTIONS

Adverse Drug 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 colitis, headache, abdominal pain, liver function test abnormal, diarrhea and nausea.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Induction of Remission, Including Clinical Remission and Mucosal Healing
In two 8-week placebo-controlled clinical studies involving 621 (Safety Population) ulcerative colitis patients, 356 received 2.4g/day or 4.8g/day MEZAVANT tablets. More adverse events occurred in the placebo group (119) than in each of the MEZAVANT treatment groups (109 in 2.4g/day, 92 in 4.8g/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 in the double-blind, placebo-controlled 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 2.4g/day, 2.2% in MEZAVANT 4.8g/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 two Phase 3, 8-week, double-blind, placebo-controlled trials are listed in Table 1.

Table 1 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] 2.4g/day n=177 (%)**	**MEZAVANT[a] 4.8g/day n=179 (%)**	**Placebo[a] n=179 (%)**
Gastrointestinal Disorders			
Flatulence	3%	2%	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.

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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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, thrombocytopenia
Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain
Nervous System Disorders: Somnolence, tremor
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal pain
Skin and Subcutaneous Tissue Disorders: Acne, rash, urticaria
Vascular Disorders: Hypertension, hypotension.

Pooled Safety Analysis

In the pooled safety analysis of patients with ulcerative colitis who participated in the clinical studies (short- and long-term, n=1368), 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 2.

Table 2 Adverse Drug Reactions Associated with MEZAVANT from Pooled Safety Analysis

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

Post-market Adverse Drug Reactions

Adverse Events Seen with MEZAVANT During Post-Marketing Surveillance

Blood and Lymphatic System Disorders: Agranulocytosis, leucopenia, neutropenia.
Cardiac Disorders: Myocarditis, pericarditis
General Disorders and Administration Site Conditions: Chest pain and discomfort
Hepatobiliary Disorders: Hepatitis
Immune System Disorder: Anaphylactic reaction, angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS)
Musculoskeletal and Connective Tissue Disorders: Lupus-like syndrome, myalgia
Nervous System Disorders: Intracranial pressure increased (see below)
Pregnancy and Fetal Outcomes: premature labor, ectrodactyly, fetal anemia, hydrops fetalis, oligohydramnios, congenital nephrotic syndrome and fetal tachycardia
Renal and Urinary Disorders: Interstitial nephritis, nephrogenic diabetes insipidus, nephrolithiasis, renal failure.
Reproductive System and Breast Disorders: Oligospermia (reversible)
Respiratory, Thoracic and Mediastinal Disorders: Acute interstitial pneumonitis, allergic alveolitis, asthma exacerbation in allergic patients, eosinophilic pneumonia, interstitial lung disease
Skin and Subcutaneous Tissue Disorders: Photosensitivity

Descriptions of Selected Adverse Reactions

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.

Additional Adverse Events Seen with Other Mesalamine Products

Blood and Lymphatic System Disorders: Aplastic anemia, pancytopenia
Hepatobiliary Disorders: Cholelithiasis
Nervous System Disorders: Neuropathy

Renal and Urinary Disorders: Nephrotic syndrome
Reproductive System and Breast Disorders: Oligospermia
Respiratory, Thoracic and Mediastinal disorders: Bronchospasm

Abnormal Hematologic and Clinical Chemistry Findings

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

DRUG INTERACTIONS

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. However, the following drug-drug interactions have been reported for products containing mesalamine:

- The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine may increase the risk of renal reactions.
- In patients receiving azathioprine or 6-mercaptopurine and/or any other drugs known to cause myelotoxicity, concurrent use of mesalamine can increase the potential for blood disorders (especially leucopenia), bone marrow failure, and associated complications.

Drug-Food Interactions

Administration of a single dose of MEZAVANT 4.8g with a high-fat meal[*] 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.

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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.[14,15,16]

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

MEZAVANT is intended for once-daily, oral administration with food. The tablets should be swallowed whole with liquid and should not be crushed or chewed.

The recommended dose for the induction of remission in patients with mild to moderate ulcerative colitis is two to four 1.2g tablets to be taken once daily for a total daily dose of 2.4 to 4.8g. No difference in remission rates was noted between doses of 2.4g/day and 4.8g/day, but trends in improvement in the sigmoidoscopy score and clinical improvement (reduction in UC-DAI from baseline of ≥3 points) was noted at 4.8g/day dose versus 2.4g/day (see **Clinical Trials**). The studies were not powered to look at differences between MEZAVANT dosing regimens of 2.4g/day and 4.8g/day. Similar efficacy was shown when a total daily dose of 2.4g of MEZAVANT was given as one dose (QD) or when given in two divided doses (BID).

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

Administration of a single dose of MEZAVANT 4.8g 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 **Drug Interactions - Drug-Food Interactions**, and **Action and Clinical Pharmacology – Pharmacokinetics, Absorption**).

Children:
The safety and effectiveness of mesalamine has not been established in children. As for tablets needing to be swallowed whole, consideration should be given to the ability to swallow the intact tablet.

Elderly:
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.

Missed Dose

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

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. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

For management of a suspected drug overdose, contact your regional Poison Control Center.

ACTION AND CLINICAL PHARMACOLOGY

The MEZAVANT tablet contains a core of mesalamine (5-aminosalicylic acid), 1.2g, formulated with MMX Multi Matrix System®* technology. 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), 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 MMX®* technology uses a matrix of lipophilic and hydrophilic excipients which, along with the gastro-resistant coating, facilitate the delayed and extended delivery of effective concentrations of mesalamine through the entire colon, with limited systemic absorption.

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

* MMX Multi Matrix System and MMX are registered trade-marks used under licence from Cosmo Technologies, Ltd.

prostaglandin production in the colon.

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.

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.

Pharmacokinetics

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 1.2g 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 2.4g or 4.8g 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 1.2g (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 4.8g, 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 4.8g 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 2.4g to 4.8g. However there was no evidence of steady-state systemic exposure increasing more than proportionately with dose.

In a single-dose study, MEZAVANT 1.2g, 2.4g and 4.8g 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 3). Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2g and 4.8g MEZAVANT. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionately between 1.2g and 2.4g and sub-proportionately between 2.4g and 4.8g MEZAVANT, with the dose-normalized value at 4.8g representing, on average, 74% of that at 2.4g based on geometric means.

Table 3 Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of MEZAVANT under Fasting Conditions

Parameter[1] of Mesalamine	**MEZAVANT 1.2g n=47**	**MEZAVANT 2.4g n=48**	**MEZAVANT 4.8g 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

Administration of a single dose of MEZAVANT 4.8g 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, 4.8g 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 4). 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 4 Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of MEZAVANT 4.8g Fasting Conditions to Young and Elderly Subjects

Parameter of 5-ASA	Young Subjects (18-35yrs) n=28	Elderly Subjects (65-75yrs) n=28	Elderly Subjects (>75yrs) 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 18L, 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 2.5mcg/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.

Excretion:
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 2.4g and 4.8g 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 **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 4.8g single dose of MEZAVANT (see **Action and 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 **Warnings and Precautions – Special Populations, Geriatrics**).

Gender:
No consistent trend on gender effect was observed in the clinical trials.

Race:
No pharmacokinetic information is available that examines MEZAVANT in different races.

Hepatic Insufficiency:
No pharmacokinetic information is available for patients with hepatic impairment (see **Warnings and Precautions – Hepatic/Biliary/Pancreatic**, **Adverse Reactions**).

Renal Insufficiency:
No pharmacokinetic information is available for patients with mild, moderate and severe renal impairment (see **Warnings and Precautions - Renal**, **Adverse Reactions**).

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.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

The MEZAVANT delayed- and extended-release tablet contains a core of 5-aminosalicylic acid (5-ASA; mesalamine), 1200mg, formulated with MMX Multi Matrix System technology. 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), 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 MMX technology uses a matrix of lipophilic and hydrophilic excipients which, along with the gastro-resistant coating, facilitate the delayed and extended delivery of effective concentrations of mesalamine through the entire colon with limited systemic absorption.

The inactive ingredients of MEZAVANT tablets are 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.

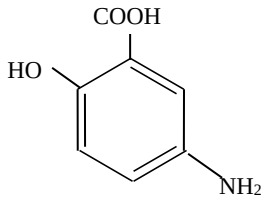
MEZAVANT tablets are supplied in opaque high density polyethylene (HDPE) bottles of 60 or 120 tablets with child-resistant closure.

PART II: SCIENTIFIC INFORMATION

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

CLINICAL TRIALS

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 2.4g/day (1.2g given twice daily) and 4.8g/day (given once daily) against placebo in 280 patients. Study SPD476-302 assessed the safety and efficacy of MEZAVANT 2.4g/day and 4.8g/day (both given once daily) against placebo in 341 patients. A pH-dependent delayed-release mesalamine 2.4g/day (administered as two 400mg 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 2.4g/day administered once daily (QD) or pH-dependent delayed-release mesalamine 1.6g/day administered as two 400mg tablets given twice daily (BID).

Study demographics and trial design

Table 5 Summary of Baseline Demographic Characteristics for Patients with Ulcerative Colitis					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Gender**
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.	2.4g/day administered as 1.2g twice daily and 4.8g/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.	2.4g/day and 4.8g/day administered once daily pH-dependent delayed-release mesalamine 2.4g/day, administered as 2x400mg 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.	2.4g/day administered once daily pH-dependent delayed-release mesalamine 1.6g/day in divided dose, administered as 0.8g 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

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 6. Both MEZAVANT 2.4g/day (1.2g given twice daily) and 4.8g/day (given once daily) demonstrated superiority over placebo. Results for study SPD476-302 are also shown in Table 6. Both MEZAVANT 2.4g/day and 4.8g/day (both given once daily) demonstrated superiority over placebo.

Table 6 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 2.4g/day BID n=88**	**MEZAVANT 4.8g/day QD n=89**	**Placebo n=86**	**MEZAVANT 2.4g/day QD n=84**	**MEZAVANT 4.8g/day QD n=85**	**pH-dependent delayed-release mesalamine[a] 2.4g/day (0.8g given TID) n=86**
Number of subjects in remission*							
n (%)	11 (12.9)	30 (34.1)	26 (29.2)	19 (22.1)	34 (40.5)	35 (41.2)	28 (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 2.4g/day twice daily and MEZAVANT 4.8g/day once daily or between MEZAVANT 2.4g/day once daily and MEZAVANT 4.8g/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 7 and Table 8). There was no statistically significant difference between MEZAVANT 2.4g/day and 4.8g/day dose groups in clinical improvement, clinical remission and sigmoidoscopic improvement; however, MEZAVANT 4.8g/day showed trends for improved efficacy over MEZAVANT 2.4g/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 7 Study SPD476-301: Secondary Efficacy Results (% Patients)

Secondary Efficacy Endpoints	**MEZAVANT 2.4g/day (Given 1.2g BID) n=88**	**MEZAVANT 4.8g/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 8 Study SPD476-302: Secondary Efficacy Results (% Patients)				
Secondary Efficacy Endpoints	**MEZAVANT 2.4g/day (Given QD) n=84**	**MEZAVANT 4.8g/day (Given QD) n=85**	**pH-dependent delayed-release mesalamine[a] 2.4g/day (0.8g 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 and rectal bleeding)*	41.7%**	41.2%**	33.7%NS	22.1%
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 9	**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 2.4g/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 2.4g/day QD (83.7%) was similar to that seen using the comparator (pH-dependent delayed-release mesalamine 1.6g/day [0.8g 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 2.4g/day administered once daily and in 2 divided doses (1.2g 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 4.8g/day dose was administered BID, and a 12-month Maintenance Phase during which MEZAVANT 2.4g/day dose was administered either (1.2g) 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 2.4g/day QD group and 92% in the MEZAVANT 1.2g BID (total 2.4g/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 2.4g/day QD group and 68.5% of subjects in the MEZAVANT 1.2g BID (total 2.4g/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 2.4g/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 2.4g/day or 4.8g/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 10.

Table 10 Principal Pharmacokinetic Parameters of 5-ASA following Administration of MEZAVANT in a 2.4g/day and 4.8g/day Single and Multiple Dose Study

Study/Dose	t_{lag} (h) (mean±SD)	t_{max} (h) (mean±SD)	C_{max} (ng/mL) (mean±SD)	AUC_{0-t} (ng.h/mL) (mean±SD)	$AUC_{0-\infty}$ (ng.h/mL) (mean±SD)	$t_{½}$ (h) (mean±SD)	% Dose absorbed
2.4g single dose n=28	5.2 ± 3.9	13.2 ± 10.0	2932 ± 2957	18573 ± 10969 (t=up to 120h)	19852 ± 11740	7.41 ± 4.65	25.2 ± 10.4
2.4g/day QD multiple dose (Day 14 data) n=28	0.0 ± 0.0	9.07 ± 5.37	2918 ± 2164	22319 ± 13697 (t=24h)	N/A	N/A	22.4 ± 9.25
4.8g single dose n=28	4.9 ± 4.2	14.4 ± 9.68	4385 ± 3033	47785 ± 22421 (t=up to 120h)	48141 ± 25627	6.28 ± 5.31	27.0 ± 12.6
4.8/day QD multiple dose (Day 14 data) n=28	0.21 ± 0.83	9.60 ± 3.78	5280 ± 3146	49559 ± 23780 (t=24h)	N/A	N/A	20.8 ± 11.6

N/A: Not Applicable

DETAILED PHARMACOLOGY

In regard to the exact mechanism of action of mesalamine, it is not clear which of the many actions of the compound is responsible for its therapeutic effects in Inflammatory Bowel Disease. For example, 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 B_4 (LTB_4), 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. However it may be a combination of all such actions, which ultimately culminates in the drug's efficacy.

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.

No animal studies of absorption, distribution, metabolism and excretion of mesalamine following administration of MEZAVANT have been conducted. However, numerous non-clinical drug metabolism and pharmacokinetic studies as well as clinical pharmacokinetics studies on various mesalamine formulations have been reported in the literature.

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500mg/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 800mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on body surface area comparison) of MEZAVANT.

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

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

Pregnancy – Teratogenic Effects:
Reproduction studies have been performed in rats at doses up to 480mg/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.

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PART III: CONSUMER INFORMATION

MEZAVANT®*

mesalamine Delayed- and Extended-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when MEZAVANT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MEZAVANT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MEZAVANT tablets contain mesalamine, which is an anti-inflammatory drug for the treatment of a flare-up of ulcerative colitis and/or to help maintain remission (mucosal healing) in patients with ulcerative colitis. Ulcerative colitis is a disease of the large bowel (colon) and back passage (rectum), where the lining of the gut becomes red and swollen (inflamed) resulting in symptoms of frequent and bloody stools together with stomach cramps.

What it does:
MEZAVANT is believed to block the production and action of certain substances (cyclooxygenase, prostaglandins and others) involved in producing inflammation. MEZAVANT tablets use a technology called MMX®**, designed to delay and deliver effective concentrations of medicine for an extended period of time throughout the colon and rectum to treat the inflammation and reduce symptoms, such as bloody stools and diarrhea.

When it should not be used:
- If you are allergic to this drug or its ingredients or components of the container (see What the nonmedicinal ingredients are)
- If you are allergic to a family of drugs known as salicylates [which includes acetylsalicylic acid (i.e., Aspirin®†)]
- If you have severe liver problems
- If you have severe kidney problems.

What the medicinal ingredient is:
mesalamine

What the nonmedicinal ingredients are:
carnauba wax, magnesium stearate, methacrylic acid – methyl methacrylate copolymer (1:1), methacrylic acid – methyl methacrylate copolymer (1:2), red ferric oxide (E172), polyethylene glycol (macrogol) 6000, 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.

What dosage forms it comes in:
MEZAVANT 1.2g delayed- and extended-release tablets are available as red-brown, oval-shaped, film-coated tablets marked on one side with “S476”.

WARNINGS AND PRECAUTIONS

BEFORE you use MEZAVANT, talk to your doctor or pharmacist if:
- You have a narrowing or blockage of the upper digestive tube (e.g., pyloric stenosis).
- You have any kidney or liver problems.
- You have chronic lung disease such as asthma or others.
- You have digestive (peptic) or duodenal ulcers.
- You have urinary tract obstructions.
- You have previously had inflammation of the heart (which may be the results of an infection of the heart).
- You have eczema (dry, itchy rashes on your skin). Your skin may be more sensitive to sunlight when taking MEZAVANT.
- You are pregnant or think that you might be pregnant. Since mesalamine crosses the placenta, care should be taken if you are taking MEZAVANT during pregnancy. Premature labor, birth defects and other adverse outcomes (such as kidney and heart issues) were reported in infants born to mothers who took MEZAVANT during pregnancy.
- You are breastfeeding or planning to breastfeed. Since mesalamine is excreted in breast milk in small quantities, care should be taken if you are taking MEZAVANT. Tell your doctor immediately if your baby experiences severe diarrhea while you are breastfeeding.
- You have had previous allergy (hypersensitivity reaction) to sulfasalazine (an ingredient in other medicines used to treat ulcerative colitis).
- You have had any allergies to this drug or its ingredients or components of the container.

Kidney stones may develop with use of mesalazine. Symptoms may include blood in urine, urinating more often, pain in your back, side, belly or groin. Be sure to drink enough liquids while you are taking MEZAVANT. Talk to your doctor about how much water or other liquids you should be drinking.

INTERACTIONS WITH THIS MEDICATION

Taking mesalamine with drugs known to affect the kidney, including some anti-inflammatory drugs (NSAIDs) and azathioprine may increase the risk of renal (kidney) reactions.

Taking mesalamine with azathioprine or 6-mercaptopurine or other drugs known to affect your bone marrow may increase your chance of having a blood disorder, bone marrow failure or other complications. Bone marrow is the material inside your bones that produces blood cells.

† Aspirin is a registered trade-mark of Bayer Aktiengesellschaft

PROPER USE OF THIS MEDICATION

Usual adult dose:
Always take MEZAVANT as your doctor has told you. This can help bring your symptoms of ulcerative colitis under control and can also reduce the risk of symptoms reappearing. You should check with your doctor or pharmacist if you are not sure.

The usual daily dose for adults is 2.4g to 4.8g (two to four tablets) taken once a day for a flare-up of ulcerative colitis.

The usual daily dose for adults to help maintain remission (mucosal healing) is 2.4g (two tablets) taken once a day.

MEZAVANT should be taken with food. The tablets should be swallowed whole with liquid and should not be chewed or crushed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take your tablets then take them as usual the next day. Do not take a double dose to make up for a forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MEZAVANT can cause side effects, although not everybody gets them. The most frequently reported adverse events within clinical studies were inflamed colon, headache, abdominal pain (stomach pain), liver function tests abnormal, loose / frequent stools (diarrhea) and nausea (feeling sick).

Other commonly reported adverse reactions or side effects (≥1% to <10%) are: painful or bloated stomach, indigestion, gas, vomiting, weakness, fever, joint pain, back pain, allergic reactions (including hives, rash and swollen face), high blood pressure, feeling sleepy or tired.

Other less common side effects (seen in less than 1 in 100 patients) are: reduced number of platelets (a blood clotting cell), exacerbation of ulcerative colitis, dizziness, rectal polyp (a non-cancerous growth in the back passage causing symptoms such as constipation and bleeding), trembling or shaking, ear or throat pain, racing heartbeat, acne, fatigue (feeling extremely tired), an inflamed pancreas (associated with pain in upper abdomen and back and feeling sick), hair loss, low blood pressure.

The following side effects have been identified with post-marketing use of MEZAVANT: low white blood cell counts, inflammation of the heart muscle and lining around the heart, inflammation of the liver, kidney problems (such as inflammation and scarring of the kidney), nephrogenic diabetes insipidus (which include passing water (urine) more often than normal and possibly at night (bed wetting), increased thirst, tiredness, loss of appetite and weight loss), inflammation of lungs due to allergic reaction, muscle pain, chest pain, allergic swelling of skin or body parts, increased pressure in brain, Lupus-Like Syndrome (which may include butterfly shaped skin rash typically on face, skin sensitivity to sunlight along with joint pain and/or arthritis), increased sensitivity to sunlight and a reversible decrease in sperm production.

The following additional side effects are associated with other medicines containing mesalamine. These are: low blood cell counts (red blood cells, white blood cells or platelets), neuropathy (abnormal or damaged nerves giving a sensation of numbness and tingling), difficulty in breathing, gall stones.

If any of the side effects become serious or persist, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	**Allergic reaction -** symptoms include hives, rash, swollen face.			√
Unknown	**Other allergic reaction -** symptoms include swelling of the mouth, throat, difficulty in breathing and worsening asthma.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	**Acute Intolerance Syndrome -** symptoms include 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** and symptoms such as unexplained bruising, unusual bleeding (for example, nose bleeds), fever, sore throat.		√	
Uncommon	**Pancreatitis** (inflamed or swollen pancreas) and symptoms such as abdominal pain and feeling sick.		√	
Rare	**Kidney problems** (such as inflammation and scarring of the kidney or kidney failure) **–** symptoms include 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)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	**Kidney stones** (hard little pebbles that form in your kidneys) – symptoms may include blood in urine, urinating more often, pain in your back, side, belly or groin.		√	
Unknown frequency	**Hepatitis** (inflammation of the liver) - symptoms include jaundice (yellowing of the skin and eyes) and flu-like symptoms.		√	
Unknown frequency	**Myocarditis/ Pericarditis** (inflammation of the heart muscle and lining around the heart) – symptoms include 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.		√	
Unknown frequency	**Hypersensitivity pneumonitis** (inflammation of lungs due to an allergic reaction) – symptoms include fever, cough, chills, and shortness of breath.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown frequency	**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			√
Unknown frequency	**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.			√
Unknown frequency	**Infant diarrhea when breastfeeding**	√		

This is not a complete list of side effects. For any unexpected effects while taking MEZAVANT, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C to 25°C).

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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 Consumer Information by visiting the Health Canada website http://hc-sc.gc.ca, the manufacturer's website www.shirecanada.com, or by calling 1-800-268-2772.

This leaflet was prepared by Shire Pharma Canada ULC.
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