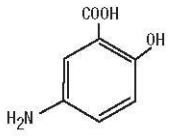
PRODUCT INFORMATION

Name of the medicine

MEZAVANT 1.2 g gastro-resistant, prolonged release tablets

Active: Mesalazine 1.2 g



Formula: $C_7H_7NO_3$
Molecular weight: 153.14
CAS number: 89-57-6

Description

MEZAVANT (mesalazine) 1.2 g gastro-resistant, prolonged release tablets contains the active ingredient, mesalazine, presented as red-brown, ellipsoidal, film-coated tablets, debossed on one side with S476.

The MEZAVANT tablet contains a core of mesalazine (5-aminosalicylic acid), 1.2g, formulated in a multi-matrix system. This system is coated with methacrylic acid copolymers, Type A and Type B, which are designed to dissolve at approximately pH 7**.** The matrix of lipophilic and hydrophilic excipients facilitates the extended delivery of effective concentrations of mesalazine through the entire colon with limited systemic absorption.

Mesalazine dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. It is very slightly soluble in water and practically insoluble in acetone, alcohol, and ether. The pKa values are 2.3 and 5.8.

Pharmacology

The mechanism of action of mesalazine 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 mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalazine 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 mesalazine may be mediated by PPAR-γ receptors.

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

Pharmacokinetics

Absorption:

Gamma-scintigraphy studies have shown that a single dose of MEZAVANT 1.2g passed rapidly and intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labelled tracer in the colon, indicating that mesalazine had spread throughout this region of the gastrointestinal tract.

The total absorption of mesalazine 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.

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 mesalazine 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 (Table 1). Mesalazine 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 (Cmax) of mesalazine increased approximately dose proportionately between 1.2g and 2.4g and sub-proportionately between 2.4g and 4.8g MEZAVANT, with the dose normalised value at 4.8g representing, on average, 74% of that at 2.4g based on geometric means.

Administration of a single dose of MEZAVANT 4.8g with a high fat meal resulted in further delay in absorption and plasma concentrations of mesalazine were detectable 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalazine (mean Cmax increased by 91%; mean AUC increased by 16%) compared to results in the fasted state. The observed differences in mesalazine exposure due to concomitant food intake are not considered to be clinically significant. Therefore, MEZAVANT can be taken without regard to food.

In a single and multiple dose pharmacokinetic study of MEZAVANT 2.4g or 4.8g was administered once daily with standard meals to 28 healthy volunteers per dose group. Plasma concentrations of mesalazine 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. The mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

Table 1: Mean (SD) PK Parameters for Mesalazine Following Single Dose Administration of MEZAVANT under Fasting Conditions

Parameter[1] of Mesalazine	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 Tmax and Tlag.

* Median (min, max); +N=43, •N=27, §N=33, #N=36, **N=46

Distribution:

Following dosing of MEZAVANT, the distribution profile of mesalazine is presumed to be the same as that for other mesalazine containing products. Mesalazine 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. Mesalazine is 43% bound to plasma proteins when in vitro plasma concentrations are 2.5μg/mL.

Metabolism:

The only major metabolite of mesalazine (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 mesalazine efficacy or toxicity.

Elimination:

Elimination of mesalazine 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 after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid.

Special patient populations:

Geriatrics: No pharmacokinetic information is available in patients who are 65 years or older

Paediatrics: No pharmacokinetic information is available in patients who are less than 18 years of age

Gender: No consistent effect of gender on MEZAVANT pharmacokinetics has been observed.

Renal Insufficiency: No pharmacokinetic information is available in patients with mild, moderate, and severe renal impairment.

Hepatic Insufficiency: No pharmacokinetic information is available for patients with hepatic impairment.

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

Clinical Trials

In two similarly designed, Phase III, placebo controlled studies (Studies SPD476-301 and SPD476-302) in 623 randomised patients with mild to moderate, active ulcerative collitis (UC), MEZAVANT 2.4g/day and 4.8g/day achieved statistical superiority over placebo in terms of the number of patients achieving remission from UC after 8 weeks of treatment. Using a modified Ulcerative Colitis Disease Activity Index (UC-DAI), remission was defined as a UC-DAI score of <1 with a score of 0 for rectal bleeding and stool frequency and at least a 1-point reduction in sigmoidoscopy score from baseline. Study 302, included a comparator, mesalazine delayed release (modified release/enteric coated) 2.4g/day TID, as an internal reference arm. Table 2 summarises the results for the primary variable of remission in the two studies.

Table 2: Summary of Efficacy Results

Study 301 (n=262[#])				
	Placebo	MEZAVANT 2.4g/day in two divided doses	MEZAVANT 4.8g/day once daily	
% patients in remission	12.9	34.1*	29.2*	
Study 302 (n=341[#])				
	Placebo	MEZAVANT 2.4g/day once daily	MEZAVANT 4.8g/day once daily	Mesalazine delayed release 2.4g/day in three divided doses
% patients in remission	22.1	40.5*	41.2*	32.6[NS]

#Based on the ITT population; * Statistically different from placebo ($p<0.025$); NS Not significant from placebo ($p>0.05$)

A randomised, open label extension study to studies 301 and 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 UC in remission over 12 months. This study (Study 303) included an 8-week Acute Extension Phase during which MEZAVANT 4.8g/day was administered BID, and a 12-month Maintenance Phase during which MEZAVANT 2.4g/day was administered either [1.2g] BID or once daily. Efficacy was a secondary objective of this uncontrolled 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 UC medication denoted by "Lack of Efficacy/Relapse." The proportion of subjects withdrawing due to a need for alternative UC 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 was approximately 88% in the MEZAVANT 2.4g/day once daily group and 92% in the MEZAVANT 2.4g/day BID group.

Remission was defined as modified UC-DAI $\leq$ 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 once daily group and 68.5% of subjects in the MEZAVANT 2.4g/day BID group met the strict remission criteria; no statistically significant differences were observed between treatment groups.

Indications

For the induction and maintenance of remission in patients with mild to moderate, active ulcerative colitis.

Contraindications

History of hypersensitivity to salicylates (including mesalazine) or any of the excipients of MEZAVANT.

Precautions

The majority of patients who are intolerant or hypersensitive to sulfasalazine can take mesalazine preparations without risk of similar reactions. However, caution should be exercised when treating patients allergic to sulfasalazine.

Following mesalazine treatment, serious blood dyscrasias have been reported rarely. 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, treatment should be terminated.

Mesalazine 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 mesalazine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required.

Mesalazine induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely with MEZAVANT and other mesalazine containing- preparations. Caution should be used in prescribing this medication to patients with conditions predisposing to the development of myo- or pericarditis. If acute intolerance syndrome is suspected,

prompt withdrawal is required and products containing mesalazine must not be reintroduced.

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

Effect on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. MEZAVANT is considered to have negligible influence on these abilities.

Effects on fertility

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalazine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison). Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with other mesalazine products during controlled clinical trials.

Use in pregnancy (Category C)

Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with non-steroidal anti-inflammatory drugs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Oral administration of mesalazine during organogenesis in rats and rabbits at respective doses up to 1,000 and 800 mg/kg/day (2 – 3 fold the maximal recommended clinical dose of MEZAVANT on a body surface area basis) was associated with embryofetal toxicity and maternotoxicity. At a dose of 1,000 mg/kg/day in rats, fetuses showed enlarged brain ventricles. There was no evidence of embryotoxicity, maternotoxicity or teratogenicity in rats and rabbits treated orally with mesalazine during the period of organogenesis at doses up to about 500 mg/kg/day.

Use in lactation

Mesalazine is excreted in breast milk at low concentration. Acetylated form of mesalazine is excreted in breast milk at higher concentration. Caution should be exercised if using Mesalazine while breast-feeding and only if the benefit outweighs the risks. Sporadically acute diarrhoea has been reported in breast fed infants.

In rats, oral administration of mesalazine during late gestation and lactation at doses of 400 and 800 mg/kg/day (similar to the maximal recommended clinical dose of MEZAVANT on a body surface area basis) was associated with toxicity to dams and offspring. A dose of 320 mg/kg/day was devoid of toxicity in either generation.

Paediatric use

MEZAVANT is not recommended for use in children below the age of 18 years due to lack of data on safety and efficacy.

Use in elderly

The usual adult dose may be used (see Dosage and Administration).

Renal impairment

Reports of renal impairment, including minimal change nephropathy, acute / chronic interstitial nephritis and renal failure have been associated with preparations containing mesalazine and pro-drugs of mesalazine. For any patient with known renal dysfunction, the risk-benefit of mesalazine treatment should be considered and caution should be exercised in these patients. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically whilst on treatment.

Hepatic Impairment

Caution is recommended if MEZAVANT is administered in patients with hepatic impairment.

Carcinogenicity

There was no evidence of carcinogenicity in mice or rats treated with mesalazine in the diet for two years at respective doses up to 2,000 and 480 mg/kg/day, associated with corresponding plasma exposures (AUC) of 8- and 3-fold clinical exposure at the maximum recommended dose of MEZAVANT.

Genotoxicity

No evidence of genotoxicity was observed in assays for bacterial gene mutation *in vitro*, mammalian cell sister chromatid exchange or chromosomal damage *in vivo*.

Interference with Laboratory Tests

Use of mesalazine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalazine's main metabolite, N-acetylaminosalicylic acid (N-Ac-5-ASA). An alternative selective assay for normetanephrine should be considered.

Interactions with other medicines

No investigations have been performed on interactions between MEZAVANT and other drugs. However, there have been reports of interactions between other mesalazine containing products and other drugs.

Caution is recommended for the concomitant use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine as these may increase the risk of renal adverse reactions.

Mesalazine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6-mercaptopurine, caution is recommended for concurrent use of mesalazine as this can increase the potential for blood dyscrasias.

Administration with coumarin-type anticoagulants e.g. warfarin, could result in decreased anticoagulant activity. Prothrombin time should be closely monitored if this combination is essential.

Adverse Effects

MEZAVANT tablets have been evaluated in 664 ulcerative colitis patients in controlled and open-label trials. In two 8-week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received 2.4g/day or 4.8g/day MEZAVANT tablets and 179 received placebo. 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 group (6.1% in placebo; 1.1% in 2.4g/day; 2.2% in 4.8g/day). The most common severe adverse events were gastrointestinal disorders which were mainly symptoms associated with ulcerative colitis. Treatment related adverse events occurring at a frequency of at least 1% in the two double blind, placebo-controlled trials are listed in Table 3.

Table 3: 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	MEZAVANT 2.4g/day (n = 177)	MEZAVANT 4.8g/day (n = 179)	Placebo (n = 179)
Headache	10 (5.6%)	6 (3.4%)	1 (0.6%)
Flatulence	7 (4%)	5 (2.8%)	5 (2.8%)
Increased alanine aminotransferase	1 (0.6%)	2 (1.1%)	0
Alopecia	0	2 (1.1%)	0
Pruritus	1 (0.6%)	2 (1.1%)	0

In a pooled safety analysis of patients with active ulcerative colitis who participated in controlled studies, the majority of subjects did not experience treatment emergent adverse events associated with MEZAVANT. Of the events reported, the majority were transient, and mild or moderate in severity. The three most frequently reported adverse drug reactions within the pooled safety analysis of the ulcerative colitis patient clinical studies were headache, abdominal pain and nausea. The common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) treatment related adverse events are listed in Table 4.

Table 4: Treatment Related Adverse Events in Controlled Clinical Studies in Patients with Ulcerative Colitis

System/Organ Class	Incidence Category	Adverse drug reaction
Blood and Lymphatic System disorders	Uncommon	Thrombocytopenia
Cardiac Disorders	Uncommon	Tachycardia
Ear and Labyrinth Disorders	Uncommon	Ear pain
Gastrointestinal Disorders	Common	Abdominal distension, abdominal pain, colitis, diarrhea, dyspepsia, flatulence, nausea, vomiting
	Uncommon	Pancreatitis, rectal polyp
General Disorders and Administration Site Disorders	Common	Asthenia, pyrexia, fatigue
	Uncommon	Face oedema
Investigations	Common	Liver-function test abnormal (e.g. ALT, AST, Bilirubin**)**
Musculoskeletal and Connective Tissue Disorders	Common	Arthralgia, back pain
Nervous System Disorders	Common	Headache
	Uncommon	Dizziness, somnolence, tremor
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Pharyngolaryngeal pain
Skin and Subcutaneous Tissue Disorders	Common	Pruritus, rash
	Uncommon	Acne, alopecia, urticaria
Vascular Disorders	Common	Hypertension
	Uncommon	Hypotension

In postmarketing experience, the following adverse reactions have been reported.

Table 5: Postmarketing Adverse Reactions

System/Organ Class	Frequency Category	Adverse Drug Reaction
Blood and Lymphatic System disorders	Uncommon	Leucopenia, neutropenia
	Rare	Agranulocytosis
Cardiac Disorders	Uncommon	Myocarditis*, pericarditis*
Hepatobiliary Disorders	Rare	Hepatitis
Immune System Disorders	Uncommon	Angioedema
	Uncommon	Anaphylactic reaction*, Stevens-Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptoms (DRESS)*
Musculoskeletal and Connective Tissue Disorders	Uncommon	Myalgia
	Not known	Lupus-like syndrome
Nervous System Disorders	Not known	Intracranial pressure increased
Renal and Urinary Disorders	Uncommon	Interstitial nephritis*
	Not known	Nephrogenic diabetes insipidus
	Rare	Renal failure
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis and eosinophilic pneumonitis)*
	Not known	Interstitial lung disease

* For adverse reactions not observed in clinical trials, the frequency was calculated as the upper limit of the 95% confidence interval of 3/X, with X representing the total sample size (n=2965) of all relevant clinical trials

Descriptions of Selected Adverse Reactions:

Intracranial pressure increased:

Cases of increased intracranial pressure with papilledema (pseudotumor cerebri or benign intracranial hypertension) have been reported with mesalazine use. If undetected, this condition may result in constriction of the visual field and permanent vision loss. Mesalazine should be discontinued, if clinically possible, if this syndrome occurs.

Nephrogenic diabetes insipidus:

Cases of nephrogenic diabetes insipidus have been reported with mesalazine use.

Dosage and Administration

MEZAVANT is intended for once daily, oral administration. The tablets must not be crushed or chewed and should be swallowed whole with or without food.

Adults, including the elderly (>65 years)

For induction of remission: 2.4 to 4.8g (two to four tablets) should be taken once daily.

For maintenance of remission: 2.4g (two tablets) should be taken once daily.

Children and adolescents

MEZAVANT is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Monitoring advice

The highest dose of 4.8g/day is recommended for patients not responding to lower doses of mesalazine. When using the highest dose (4.8g/day), the effect of the treatment should be evaluated at 8 weeks.

Dosage adjustment

Specific studies have not been performed to investigate MEZAVANT in patients with hepatic or renal impairment, dialysis or concomitant disease.

Overdosage

MEZAVANT is an aminosalicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration as a result of sweating, diarrhoea and vomiting, hypoglycaemia, hyperventilation, disruption of electrolyte balance and blood-pH and hyperthermia.

Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Hypoglycaemia, fluid and electrolyte imbalance should be corrected by the administration of appropriate therapy. Adequate renal function should be maintained.
For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 131126).

Presentation

Tablets are packed in polyamide/aluminium/PVC foil blister packs with aluminium push-through foil. Pack size 60 or 120 tablets. Not all sizes may be marketed.

The tablets are presented as red-brown, ellipsoidal, film-coated tablets, debossed on one side with S476.

Composition

Active: Mesalazine 1.2 g

Excipients: Carmellose sodium, Carnauba Wax, Stearic Acid, Silicon Dioxide, Sodium Starch Glycollate, Talc-purified, Magnesium Stearate, Methacrylic Acid Copolymer, Triethyl citrate, Titanium Dioxide (E171), Iron Oxide Red (CI77491), Macrogol 6000.

Storage conditions

Store below 25°C. Store in the original package.

Poison Schedule

S4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

25 September 2009

Date of most recent amendment

2 May 2017

Sponsor

Shire Australia Pty Limited
Level 39
225 George Street
Sydney, NSW 2000
Australia