Approved professional information for MEZAVANT

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MEZAVANT, 1200 mg, enteric coated, prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated, prolonged-release tablet contains 1200 mg mesalazine.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated, prolonged-release tablets.

Red-brown, ellipsoidal, film-coated tablet, embossed on one side with S476.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEZAVANT is indicated for the treatment and maintenance of remission in ulcerative colitis.

4.2 Posology and method of administration

Posology

Adults, including the elderly (> 65 years)

For induction of remission: 2,4 to 4,8 g (two to four tablets) should be taken once daily. The highest dose of 4,8 g/day is recommended for patients not responding to lower doses of MEZAVANT. When using the highest dose (4,8 g/day), the effect of the treatment should be evaluated at 8 weeks.

For maintenance of remission: 2,4 g (two tablets) should be taken once daily.

Special populations

Hepatic or renal impairment

Specific studies have not been performed to investigate MEZAVANT in patients with hepatic or renal impairment (see section 4.3 and section 4.4).

Paediatric population

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

Method of administration

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

4.3 Contraindications

- History of hypersensitivity to salicylates (including mesalazine) or any of the excipients of MEZAVANT.
- Severe renal impairment (GFR < 30 mL/min/1,73 m^2) and/or severe hepatic impairment.

4.4 Special warnings and precautions for use

- Use in the elderly should be cautious and subject to patients having a normal renal function.
- Reports of renal impairment, including minimal change nephropathy, and acute/chronic interstitial nephritis have been associated with MEZAVANT. MEZAVANT should be used with caution in patients with confirmed mild to moderate renal impairment. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and at least twice a year, whilst on treatment.

- Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions and should be closely monitored.
- Following MEZAVANT treatment, serious blood dyscrasias have been reported. 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. MEZAVANT induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported. Caution should be used in prescribing MEZAVANT to patients with conditions predisposing to the development of myo- or pericarditis. If such hypersensitivity reaction is suspected, MEZAVANT must not be reintroduced.
- MEZAVANT 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 sulphasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required and MEZAVANT must not be reintroduced.
- There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine such as MEZAVANT. Caution is recommended if MEZAVANT is administered to patients with hepatic impairment.
- Caution should be exercised when treating patients allergic to sulphasalazine due to the potential risk of cross sensitivity reactions between sulphasalazine and mesalazine.
- Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of MEZAVANT.
- Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100 % mesalazine content. Ensure adequate fluid intake during treatment.

Porphyria

Safety has not been established.

4.5 Interactions with other medicines and other forms of interaction

The following drug interactions have been reported for medicines containing mesalazine:

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.

In patients receiving azathioprine or 6-mercaptopurine, and/or any other medicines known to cause myelotoxicity, concurrent use of mesalazine can increase the potential for blood dyscrasias, bone marrow failure and associated complications.

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.

Paediatric population

Interaction studies have not been performed in paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Mesalazine is known to cross the placental barrier.

Congenital malformations and other adverse outcomes (including one event of hydrops fetalis and foetal anaemia in one infant) were reported in infants born to mothers who were exposed to mesalazine during pregnancy.

Breastfeeding

Low concentrations of mesalazine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. Acute diarrhoea has been reported in breastfed infants of mothers exposed to mesalazine. MEZAVANT is not recommended for mothers breastfeeding their infants.

Fertility

Data on MEZAVANT shows no sustained effect on male fertility.

4.7 Effects on ability to drive and use machines

No currently available data suggest that MEZAVANT affects the ability to drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Approximately 14 % of subjects experienced treatment emergent adverse drug reactions (ADRs) associated with MEZAVANT.

The most frequently reported ADRs during acute treatment were colitis, abdominal pain, liver function test abnormal, diarrhoea, flatulence, nausea or headache, which were not dose related and occurred in less than 3 % of patients receiving MEZAVANT.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Frequent	Hypersensitivity (including rash, pruritis, urticaria and facial oedema).

	Frequency unknown	Anaphylactic reaction, drug reaction with eosinophilia and systemic symptoms (DRESS).
Nervous system disorders	Frequent	Headache.
	Less frequent	Dizziness, somnolence.
Cardiac disorders	Less frequent	Tachycardia.
Vascular disorders	Less frequent	Hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders	Less frequent	Pharyngolaryngeal pain.
Gastrointestinal disorders	Frequent	Flatulence, nausea, abdominal distension, abdominal pain, colitis, diarrhoea, dyspepsia, vomiting.
	Less frequent	Pancreatitis, rectal polyp.
Hepato-biliary disorders	Frequent	Abnormal liver function test (eg. ALT, AST, bilirubin).
	Less frequent	Increased alanine aminotransferase.
Skin and subcutaneous tissue disorders	Less frequent	Acne, alopecia, prurigo, pruritus, rash, urticaria.
	Frequency unknown	Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, back pain
Renal and urinary disorders	Less frequent	Renal failure, nephrolithiasis.
General disorders and administration site conditions	Frequent	Asthenia, face oedema, fatigue, pyrexia.
	Less frequent	Face oedema.

MEZAVANT has also been associated with the following events (post-marketing):

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Blood and lymphatic system disorders	Frequency unknown	Agranulocytosis, aplastic anaemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia.
Immune system disorders	Frequency unknown	Angioedema, anaphylactic reaction, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS).
Nervous system disorders	Frequency unknown	Neuropathy, intracranial pressure increased.
Cardiac disorders	Frequency unknown	Myocarditis, pericarditis.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Allergic alveolitis, bronchospasm, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), interstitial lung disease.
Hepato-biliary disorders	Frequency unknown	Cholelithiasis, hepatitis.
Skin and subcutaneous tissue disorder	Frequency unknown	Photosensitivity.
Musculoskeletal and connective tissue disorders	Frequency unknown	Lupus-like syndrome, myalgia.
Renal and urinary disorders	Frequency unknown	Renal failure, interstitial nephritis, nephrotic syndrome, nephrogenic diabetes insipidus.
Reproductive system and breast disorders	Frequency unknown	Oligospermia (reversible)

c. Description of selected adverse reactions

Intracranial pressure increased:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.11 Medicines acting on the Gastro-intestinal tract

Pharmacotherapeutic group and ATC code: Aminosalicyclic acid and similar agents, A07EC02

Mechanism of action

Mesalazine (5-aminosalicylic acid) is a salicylate that is used for its local effects in the treatment of inflammatory bowel disease.

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.

Pharmacodynamic effects

The pharmacodynamic action of mesalazine occurs in the colonic/rectal mucosae local to the delivery of the medicine from MEZAVANT into the lumen.

There is information suggesting that the severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mesalazine. However, plasma concentrations representing systemically absorbed mesalazine are not believed to contribute extensively to efficacy.

5.2 Pharmacokinetic properties

Absorption

Gamma-scintigraphy studies have shown that a single dose of MEZAVANT 1,2 g 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. Complete disintegration of MEZAVANT and

complete release of mesalazine occurred after approximately 17,4 hours.
The total absorption of mesalazine from MEZAVANT 2,4 g or 4,8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22 % of the administered dose.

In a single-dose study, MEZAVANT 1,2 g, 2,4 g, and 4,8 g were administered in the fasted state to healthy subjects. Plasma concentrations of 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. Mesalazine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was dose proportional between 1,2 g and 4,8 g MEZAVANT. Maximum plasma concentrations (C_{max}) of mesalazine increased approximately dose proportionally between 1,2 g and 2,4 g and disproportionally between 2,4 g and 4,8 g MEZAVANT, with the dose-normalized value at 4,8 g representing, on average, 74 % of that at 2,4 g based on geometric means.

Administration of a single dose of MEZAVANT 4,8 g with a high fat meal (SPD476-106) 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 C_{max}: ↑91 %; mean AUC: ↑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 relevant. Therefore, MEZAVANT can be taken without regard to food.

In a single- and multiple-dose pharmacokinetic study of MEZAVANT, 2,4 g or 4,8 g 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. Mean AUC at steady state was only modestly greater (1,1- to 1,4-fold) than predictable from single-dose pharmacokinetics.

In a single-dose pharmacokinetic study of MEZAVANT, 4,8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young [18-35 years], 28 elderly [65-75 years], 15 elderly [> 75 years]). Increased age resulted in increased systemic exposure (up to approximately 2-fold, based on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) to mesalazine and its metabolite N-acetyl-5-aminosalicylic acid, but did not affect the percentage of mesalazine absorbed. Increased age resulted in a slower apparent elimination of mesalazine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Distribution

Following dosing of MEZAVANT, mesalazine has a small volume of distribution of approximately 18 L. Mesalazine is 43 % bound to plasma proteins when *in vitro* plasma concentrations were 2,5 µg/mL.

Metabolism

The metabolism of mesalazine takes place by acetylation. The only major metabolite of mesalazine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid, which is pharmacologically inactive. The metabolite formation occurs 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). 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. The terminal half-lives for mesalazine and its major metabolite after administration of MEZAVANT 2,4 g and 4,8 g were, on average, 7-9 hours and 8-12 hours, respectively.

Paediatrics

No pharmacokinetic study was conducted in paediatrics.

Elderly

Systemic exposure to mesalazine increased by up to 2-fold in elderly subjects (> 65 years) compared with younger adult subjects (18-35 years) after a 4,8 g single dose of MEZAVANT. Systemic exposures in individual subjects were inversely correlated to 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 section 4.4).

Renal Impairment

Systematic pharmacokinetic study was not conducted in subjects with renal impairment.

Hepatic Impairment

Systematic pharmacokinetic study was not conducted in subjects with hepatic impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium;

carnauba wax;

silica, colloidal hydrated;

macrogol 6000;

magnesium stearate;

methacrylic acid copolymer;

red ferric oxide (E172);

sodium starch glycolate;

stearic acid;

talc;

titanium dioxide (E171);

triethylcitrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in outer container until before use.

6.5 Nature and contents of container

MEZAVANT tablets are packed in blisters strips of 12 tablets per blister.

Polyamide/aluminium/PVC foil with aluminium push-through foil blisters in packs of 60 tablets per pack and 120 tablets per pack. The blister strips are packaged in outer unit cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

ADCOCK INGRAM LIMITED

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8. REGISTRATION NUMBER(S)

Registration number: 45/11/0463

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2013

10. DATE OF REVISION OF THE TEXT

20 May 2022