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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.

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4.2 Posology and method of administration Posology

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.

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.

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

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necrolysis (TEN), have been reported in association with **MEZAVANT** treatment. **MEZAVANT** should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

- **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.
- Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.
- 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.

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose (4 tablets), essentially ‘sodium-free’.

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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, Nacetylaminosalicylic acid (N-Ac-5-ASA). An alternative selective assay for normetanephrine should be considered.

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

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.
- 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
- Mesalazine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6-mercaptopurine, and/or any other medicines known to cause myelotoxicity, concurrent use

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of mesalazine can increase the potential for blood dyscrasias, bone marrow failure and associated complications.

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 foetalis and foetal anaemia in one infant) were reported in infants born to mothers who were exposed to mesalazine during pregnancy.

Breast-feeding

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 breast-fed infants of mothers exposed to mesalazine. **MEZAVANT** is not recommended for mothers breast-feeding their infants.

Fertility

Data on **MEZAVANT** shows no sustained effect on male fertility.

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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

The most frequently reported adverse drug reactions (ADRs) within the pooled safety analysis of clinical studies with Mezavant, including 3,611 patients, were colitis (including ulcerative colitis) 5,8 %, abdominal pain 4,9 %, headache 4,5 %, liver function test abnormal, 2,1 %, diarrhoea 2,0 %, and nausea 1,9 %.

Adverse reactions are listed by System Organ Class (see table below). Within each system organ class, adverse reactions are listed under headings of frequency using the categories: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

Adverse Drug Reactions (ADRs) Associated with Mezavant		
System/Organ Class	**Incidence Category**	**Adverse drug reaction**
Blood and lymphatic system	Uncommon	Thrombocytopenia*

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disorders	Rare	Agranulocytosis*
	Not known	Aplastic anaemia*, Leukopenia*, Neutropenia*, Pancytopenia*
Immune system disorders	Uncommon	Face oedema
	Not known	Hypersensitivity*, Anaphylactic shock, Angioedema
Nervous system disorders	Common	Headache*
	Uncommon	Dizziness, Somnolence, Tremor
	Not known	Idiopathic intracranial hypertension*, neuropathy
Ear and labyrinth disorders	Uncommon	Ear pain
Cardiac disorders	Uncommon	Tachycardia
	Not known	Myocarditis*, Pericarditis*
Vascular disorders	Common	Hypertension
	Uncommon	Hypotension

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Respiratory, thoracic and mediastinal disorders	Uncommon	Pharyngolaryngeal pain*
	Not known	Hypersensitivity pneumonitis (including interstitial Pneumonitis, allergic alveolitis, eosinophilic pneumonitis), Bronchospasm
Gastrointestinal disorders	Common	Abdominal distension, Abdominal pain*, Colitis, Diarrhoea*, Dyspepsia, Vomiting, Flatulence, Nausea
	Uncommon	Pancreatitis, Rectal polyp
Hepatobiliary disorders	Common	Liver Function Test abnormal* (e.g., ALT; AST, Bilirubin)
	Not known	Hepatitis, Hepatotoxicity, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Pruritus, Rash*
	Uncommon	Acne, Alopecia, Urticaria,
	Rare	Photosensitivity
	Not known	Stevens-Johnson syndrome (SJS)*, toxic epidermal necrolysis (TEN)*, drug reaction with eosinophilia and

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		systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Back pain
	Uncommon	Myalgia
	Not known	Systemic-lupus erythematosus-like syndrome, Lupus-like syndrome
Renal and urinary disorders	Rare	Renal failure*
	Not known	Interstitial nephritis*, Nephrotic syndrome*, Nephrolithiasis*
Reproductive system and breast disorders	Not known	Oligospermia (reversible)
General disorders and administration site conditions	Common	Asthenia, Fatigue, Pyrexia*

See section 4.4.

c. Description of selected adverse reactions

Photosensitivity

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More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and, systemic symptoms (DRESS), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

4.9 Overdose

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

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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 proliferatoractivated receptors) may be implicated in ulcerative colitis. PPAR- γ receptor agonists have shown efficacy

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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.

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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.

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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-5aminosalicylic 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-5aminosalicylic acid (acetylation). Of the approximately 21-22 % of the dose absorbed, less than

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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.

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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.

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Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Takeda (Pty) Ltd

Building A, Monte Circle,

64 Montecasino Boulevard

Fourways, 2191

Tel: 011 514 300

8. REGISTRATION NUMBER(S)

Registration number: 45/11/0463

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2013

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10. DATE OF REVISION OF THE TEXT

20 May 2026