SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PENTASA® 500 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mesalazine.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablets.

White grey to pale brown, speckled round tablets. Breakmark and embossing: 500 mg on one side, PENTASA on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PENTASA® 500 mg prolonged-release tablets are used for the treatment of mild to moderate ulcerative colitis and maintenance of remission of ulcerative colitis.

4.2 Posology and method of administration

Posology

Ulcerative colitis:

Treatment of active disease:

Adults: Individual dosage, up to 4 g mesalazine once daily or in divided doses.

Maintenance treatment:

Adults: Individual dosage, recommended dosage, 2 g mesalazine once daily or in divided doses.

Paediatric population

The safety and efficacy in children below 6 years of age have not been established.

There is only limited documentation for an effect in children (age 6-18 years).

Ulcerative colitis:

Treatment of active disease:

Children 6 years and older: to be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:

Children 6 years and older: to be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

Method of administration

Oral use.

The tablet must not be crushed or chewed. The tablet may be swallowed whole or, to facilitate swallowing, the tablets may be dispersed in 50 mL of cold water. Stir and drink immediately.

4.3 Contraindications

- Hypersensitivity to mesalazine, salicylates or to any of the excipients listed in section 6.1.
- Severe liver impairment.
- Severe renal impairment with a GFR < 30 mL/min per 1,73 m^2.

4.4 Special warnings and precautions for use

Caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). Severe

cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment such as PENTASA® 500 mg. In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever and severe headache and/or the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other signs of hypersensitivity, PENTASA® 500 mg should be discontinued immediately.

Caution is recommended in patients with mild to moderate impaired liver function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating doctor. (See section 4.3).

PENTASA® 500 mg is not recommended for use in patients with mild and moderate renal impairment, GFR 30-80 mL/min per 1,73 m^2 (see section 4.3), and in patients with haemorrhagic diathesis.
Renal function should be monitored regularly in all patients (e.g., serum creatinine), especially during the initial phase of treatment. Urinary status (dip sticks) should be determined prior to and during treatment at the discretion of the treating doctor. PENTASA® 500 mg induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.
The concurrent use of other known nephrotoxic medicines, i.e., NSAID's and azathioprine, may increase the risk of renal reactions and increased monitoring frequency of renal function, as appropriate, is essential.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with PENTASA® 500 mg (refer to section 4.8).
Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported. Blood dyscrasias have been reported (see section 4.5). Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating doctor. Concomitant treatment with PENTASA® 500 mg can increase the risk of blood dyscrasia in patients receiving azathioprine, or 6-mercaptopurine or thioguanine (see section 4.5). Treatment should be discontinued on suspicion or evidence of these adverse reactions. Symptoms can include bleeding,

bruises, sore throat, and fever or, in case of inflammation of the cardiac muscle and pericardium, fever and chest pain accompanied by shortness of breath.

Idiopathic intracranial hypertension

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 (as contained in PENTASA® 500 mg) should be considered.

Cases of nephrolithiasis have been reported with the use of mesalazine (as contained in PENTASA® 500 mg) including stones with a 100 % mesalazine content. It is recommended to ensure adequate fluid intake during treatment.
As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional symptoms occur, these tests should be performed immediately.

Mesalazine (as contained in PENTASA® 500 mg) may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches).

PENTASA® 500 mg should be used with caution in the elderly.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed. Patients who are concomitantly treated with azathioprine, or 6-mercaptopurine, or thioguanine, have shown a higher frequency of myelosuppressive effects of azathioprine, or 6-mercaptopurine, or thioguanine should be taken into account. Combination therapy with PENTASA® 500 mg tablets can increase the risk of blood dyscrasia in patients. Regular monitoring of white blood cells is recommended and the dosage regimen of thiopurines should be adjusted accordingly. (See section 4.4).

PENTASA® 500 mg tablets might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

PENTASA® 500 mg may be used with caution during pregnancy or by women who are breastfeeding their infants. The underlying condition itself (inflammatory bowel disease [IBD]) may increase risks for adverse pregnancy outcome.

Pregnancy

Mesalazine is known to cross the placental barrier and its concentration in umbilical cord plasma is lower than the concentration in maternal plasma. The metabolite acetyl-mesalazine is found at similar concentrations in umbilical cord and maternal plasma. There are no adequate and well-controlled studies of PENTASA® 500 mg use in pregnant women.

However, limited published human data on mesalazine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease. To date no other relevant epidemiologic data are available.

In one single case after long-term use of a high dose (2-4 g, orally) of mesalazine as contained in PENTASA® 500 mg during pregnancy, renal failure in a neonate was reported.

Animal studies on oral PENTASA® do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Blood disorders (pancytopaenia, leukopaenia, thrombocytopaenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA® 500 mg.

Breastfeeding

Mesalazine is excreted in breast milk. The mesalazine concentration in breast milk is lower than in maternal blood, whereas the metabolite, acetyl-mesalazine, appears in similar or increased concentrations.

There is limited experience of the use of oral mesalazine in lactating women. No controlled studies with PENTASA®

500 mg during breastfeeding have been carried out.

Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. If the infant develops diarrhoea, breastfeeding should be discontinued.

Fertility

Animal data on mesalazine show no effect on male and female fertility.

4.7 Effects on ability to drive and use machines

Treatment with PENTASA® 500 mg has no or negligible influence on the ability to drive and/or use machines.

4.8 Undesirable effects

The most frequent adverse reactions seen in clinical trials are diarrhoea (3 %), nausea (3 %), abdominal pain (3 %), headache (3 %), vomiting (1 %) and rash (1 %).

Hypersensitivity reactions and drug fever may occur.

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment such as PENTASA® 500 mg (see section 4.4).

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance

System Organ Class (SOC)	**Common (≥ 1/100 to < 1/10)**	**Rare (≥ 1/10 000 to < 1/1 000)**	**Very rare (< 1/10 0000)**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Altered blood counts (anaemia, aplastic anaemia,	

			leukopaenia [including granulocyto-paenia], neutropaenia, thrombo-cytopaenia, agranulocytosis, pancytopaenia, eosinophilia [as part of an allergic reaction])	
Immune system disorders			Hypersensitivity reaction including allergic exanthema, anaphylactic reaction, lupus erythematosus syndrome	
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy	Idiopathic intracranial hypertension (see section 4.4)
Cardiac disorders		Myocarditis *, pericarditis *		
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (including dyspnoea,	

			coughing, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, vomiting, flatulence	Increased amylase (blood and/or urine), acute pancreatitis *	Pancolitis	
Hepato-biliary disorders			Increase in transaminases, cholestasis parameters (e.g., alkaline phosphatase, gamma-glutamyl transferase and bilirubin), hepatotoxicity (including hepatitis *, cholestatic hepatitis, cirrhosis,	

			hepatic failure)	
Skin and subcutaneous tissue disorders	Rash (including urticaria, erythema-tous rash)	Photosensitivity **	Reversible alopecia, erythema multiforme	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, arthralgia	
Renal and urinary disorders			Renal function impairment (including acute and chronic interstitial nephritis *, nephrotic syndrome, renal insufficiency)	Nephrolithiasis ***, urine discolouration ***
Reproductive system and breast disorders			Oligospermia (reversible)	
General disorders and administration site conditions			Drug fever	

(*) The mechanism of mesalazine-induced myo- and pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

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

(***) See section 4.4 for further information.

It is important to note that several of these disorders can also be attributed to the inflammatory bowel disease itself.

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is limited clinical experience with overdose of PENTASA® 500 mg which does not indicate renal or hepatic toxicity.

Symptoms of overdosage include those of salicylism e.g., dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, mental confusion, hyperventilation, fever, restlessness, ketosis, respiratory alkalosis, and metabolic acidosis. Depression of the central nervous system may lead to coma; cardiovascular collapse and respiratory failure.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.11 Medicines acting on gastrointestinal tract.

Pharmacotherapeutic group: Intestinal anti-inflammatory agents.

ATC code: A07 EC02 Aminosalicylic acid and similar agents

PENTASA® 500 mg is mesalazine (5-amino salicylic acid) contained in micro-granules in a tablet formulation.

The effect of mesalazine after oral administration is unknown but appears to be due to a local effect on the inflamed

intestinal tissue, rather than to a systemic effect.

Mesalazine has *in-vitro* and *in-vivo* pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leukotriene production, and scavenge of free radicals.

5.2 Pharmacokinetic properties

PENTASA® prolonged release tablets consist of ethylcellulose-coated micro-granules of mesalazine. Following administration and tablet disintegration mesalazine is continuously released from the individual micro-granules throughout the gastrointestinal tract in any enteral pH conditions. The micro-granules enter the duodenum within an hour of administration, independent of food co-administration. The average small intestine transit time is approximately 3-4 hours in healthy individuals.

Biotransformation:

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl-mesalazine (acetyl-mesalazine). Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient. Acetyl-mesalazine is thought to be clinically inactive.

Absorption:

Based on urine recovery data in healthy volunteers, 30-50 % of the ingested dose is absorbed following oral administration, predominantly from the small intestine. Mesalazine is detectable in plasma already 15 minutes following administration. Maximum plasma concentrations are seen 1-4 hours post-dose. After a gradual decrease, mesalazine is no longer detectable 12 hours post-dose. The plasma concentration curve for acetyl-mesalazine follows the same pattern, but the concentrations are generally higher, and the elimination is slower. The metabolic ratio of acetyl-mesalazine to mesalazine in plasma after oral administration ranges from 3,5 to 1,3 after daily doses of 500 mg x 3 and 2 g x 3, respectively, implying a dose-dependent acetylation which may be subject to saturation. Mean steady-state plasma concentrations of mesalazine are approximately 2 micromoles/L, 8 micromoles//L and 12 micromoles//L after 1,5 g, 4 g, and 6 g daily dosages, respectively. For acetyl-mesalazine the corresponding concentration are 6

micromoles//L, 13 micromoles//L and 16 micromoles//L.

The transit and release of mesalazine after oral administration are independent of food co-administration.

Distribution:

Mesalazine and acetyl mesalazine do not cross the blood-brain barrier. Protein binding of mesalazine is approximately 50 % and of acetyl-mesalazine about 80 %.

Elimination:

The plasma half-life of pure mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes. Due to the continuous release of mesalazine from PENTASA® throughout the gastrointestinal tract, the elimination half-life cannot be determined after oral administration. However, steady-state is reached after a treatment period of 5 days following oral administration. Both substances are excreted in the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone

Ethylcellulose

Magnesium stearate

Talc

Microcrystalline cellulose

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C; in the original package, protected from light. Do not freeze.

6.5 Nature and contents of container

Pack sizes of 100 tablets in double aluminium foil blisters, each strip containing 10 tablets; packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

33/11/0088

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 May 2001

10 DATE OF REVISION OF THE TEXT

Type IA_{IN} Implementable 7 January 2026

Namibia Reg. No./Nr: 04/11/0848