SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PENTASA® SACHETS 2 g Prolonged release granules

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2 g or 4 g mesalazine.

PENTASA® SACHETS are sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release granules.

White-grey to pale white-brown, cylindrical shaped granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PENTASA® SACHETS is indicated in adults and children age 6 years and over for:

- The treatment of mild to moderate ulcerative colitis and the maintenance of remission in ulcerative colitis.
- The treatment of mild to moderate Crohn's disease (CDAI score 200 to 400).

4.2 Posology and method of administration

Posology

Ulcerative colitis:

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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. Can also be taken in divided doses.

Crohn's disease:

Active and maintenance treatment for adults:

Individual dosage, up to 4 g mesalazine daily in divided doses.

Paediatric population

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

Ulcerative colitis:

Treatment of active disease:

Children 6 years of age 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 of age 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 with a body weight of up to 40 kg; and the normal adult dose to those above 40 kg.

Crohn's disease:

Treatment of active disease:

Children 6 years of age and older: To be determined individually, starting with 30 - 50 mg/kg/day in divided

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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 of age and older: To be determined individually, starting with 15 - 30 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (recommended adult dose).

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

Method of administration

PENTASA® granules must not be chewed. The contents of the sachet should be emptied on the tongue and swallowed with water or juice. Alternatively, the entire content of the sachet can be taken with yogurt and consumed immediately.

4.3 Contraindications

- Hypersensitivity to mesalazine, salicylates or to any of the excipients listed in section 6.1.
- Severe liver and/or renal impairment.

4.4 Special warnings and precautions for use

Caution is recommended in patients allergic to sulfasalazine (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® SACHETS. In case of acute symptoms of intolerance i.e., abdominal cramps, acute abdominal pain, fever, 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, the treatment should be discontinued immediately.

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

PENTASA® SACHETS is not recommended for use in patients with renal impairment. Renal function should be monitored regularly (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® SACHETS induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. With concurrent use of other known nephrotoxic medicines, such as NSAIDs and azathioprine, renal function should be monitored more frequently.
Caution is recommended in patients with active peptic ulcer.

Patients with pulmonary disease, in particular asthma, should be carefully monitored during a course of treatment; please refer to section 4.8.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported. Serious blood dyscrasias have been reported with PENTASA® SACHETS (see section 4.5). Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating doctor. 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 myocarditis and pericarditis, 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

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hypertension occurs, discontinuation of mesalazine (as contained in PENTASA® SACHETS) should be considered.

Cases of nephrolithiasis have been reported with the use of mesalazine (as contained in PENTASA® SACHETS) 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.

PENTASA® SACHETS should be used with caution in the elderly.

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

4.5 Interaction with other medicines and other forms of interaction

Combination therapy with azathioprine or 6-mercaptopurine or thioguanine have shown a higher frequency of myelosuppressive effects, and an interaction cannot be ruled out, however, the mechanism behind the interaction is not established. Regular monitoring of white blood cells is recommended and dosage regime of thiopurines should be adjusted accordingly.

PENTASA® SACHETS might decrease the anticoagulant effect of warfarin.

The concurrent use of other known nephrotoxic medicines such as NSAIDs and azathioprine may increase

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the risk of renal reactions (see 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

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

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, parturition or postnatal development.

Blood disorders (pancytopenia, leukopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA® SACHETS.

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

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PENTASA® SACHETS 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® SACHETS is unlikely to affect the ability to drive and/or use machines.

4.8 Undesirable effects

The most frequent side effects seen in clinical trials were diarrhoea, nausea, abdominal pain, headache, vomiting and rash.

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® SACHETS (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, leukopenia	

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			(including granulocytopenia), neutropenia, thrombocytopenia, agranulocytosis, pancytopenia, eosinophilia (as part of an allergic reaction))	
Immune system disorders			Hypersensitivity reaction including anaphylactic reaction	
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy, idiopathic intracranial hypertension (see section 4.4)	
Cardiac disorders		Myocarditis*, pericarditis*	Pericardial effusion	
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,	Increased amylase, acute pancreatitis*	Pancolitis	

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	nausea, vomiting, flatulence			
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, erythematous rash)	Photosensitivity**	Alopecia (reversible), Quincke's oedema, dermatitis allergic, erythema multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders			Myalgia, arthralgia, lupus erythematosus-like syndrome (systemic lupus erythematosus)	
Renal and urinary disorders			Renal function impairment (including	Nephrolithiasis***

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			acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency), urine discolouration***	
Reproductive system and breast disorders			Oligospermia (reversible)	
General disorders			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 asked 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® SACHETS which does not indicate renal or hepatic toxicity. Since PENTASA® SACHETS is an amino salicylate, symptoms of salicylate toxicity, such as acid-base balance disorder, hyperventilation, pulmonary oedema, vomiting, dehydration

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and hypoglycaemia, may occur. Symptoms of salicylate overdosage are well described in the literature.

There have been reports of patients taking oral daily doses of 8 grams for a month without any adverse events.

There is no specific antidote and treatment is symptomatic and supportive. The treatment at hospital includes close monitoring of renal function.

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

Mesalazine inhibits the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism, thereby decreasing the production of prostaglandins, leukotrienes and hydroxyeicosatetraenoic acids.

Mesalazine may also reduce neutrophil and macrophage chemotaxis and phagocytosis and inhibits cytokine production and immunoglobulin secretion by peripheral blood and intestinal mononuclear cells.

Mesalazine or 5-amino-salicylic acid has a local effect on the inflamed intestinal tissue of the gastrointestinal tract, rather than a systemic effect.

5.2 Pharmacokinetic properties

General characteristics

PENTASA® SACHETS prolonged release granules consist of ethylcellulose-coated microgranules of mesalazine. Following administration mesalazine is released continuously from the individual microgranules from the duodenum to the rectum at any enteral pH conditions. One hour after oral administration the microgranules are present in the duodenum, independently of food co-administration. The average small intestinal transit time is approximately 3-4 hours in healthy volunteers.

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Biotransformation

Mesalazine is metabolised into N-acetyl-mesalazine (acetyl-mesalazine) both pre-systemically by the intestinal mucosa and systemically in the liver. Some acetylation also takes place by colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient. Acetyl-mesalazine is believed to be clinically as well as toxicologically inactive.

Absorption

Based on urine recovery data in healthy volunteers, 30 – 50 % of an oral dose is absorbed, predominantly from the small intestine.

Mesalazine is detectable in plasma 15 minutes after administration. Maximum plasma concentrations are seen 1 – 4 hours post-dose. The plasma concentration of mesalazine decreases gradually and is no longer detectable 12 hours post-dose. The plasma concentration curve for acetyl-mesalazine follows the same pattern, but the concentration is generally higher, and the elimination is slower.

Distribution

Protein binding of mesalazine is approximately 50 % and of acetyl-mesalazine about 80 %.

Elimination

The plasma half-life of 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. Both mesalazine and acetyl-mesalazine are excreted in the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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Ethylcellulose

Povidone

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C in the original package. Protect from light.

6.5 Nature and contents of container

The granules are filled into tight, polyester/aluminium/LD polyethylene sachets.

Pack sizes:

2 g sachet: 10 or 60 sachets are placed into a cardboard carton.

4 g sachet: 10, 20, 30, 50 or 100 sachets are placed into a cardboard carton.

Not all pack sizes may be marketed.

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

Ferring (Pty) Ltd

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8 REGISTRATION NUMBERS

Pentasa Sachets 2 g: 43/11/0014

Pentasa Sachets 4 g: 56/11/1135.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Pentasa Sachets 2 g: 02 October 2014

Pentasa Sachets 4 g: 01 October 2024.

10 DATE OF REVISION OF THE TEXT

Type IA_{IN} Implementable 7 January 2026

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