SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PENTASA® 1 g Suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **PENTASA® 1 g Suppository** contains 1 g mesalazine.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories.

White to tan, spotted, oblong suppositories.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PENTASA® 1 g Suppositories are used for the treatment of mild to moderate ulcerative proctitis where the lesions are within 30 cm of the anal verge.

4.2 Posology and method of administration

Posology

Ulcerative proctitis:

Acute Treatment:

One suppository (1 g) daily.

Maintenance Treatment:

One suppository (1 g) three times weekly, on non-consecutive days.

Paediatric population

Not recommended in children and adolescents. There is little experience and only limited documentation for an effect in children.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Blood tests (differential blood count) should be determined prior to and during treatment, at the discretion of the treating physician.

Caution is recommended in patients with impaired hepatic function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.

PENTASA® 1 g Suppositories should not be used in patients with impaired renal function. The 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 physician. Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The concurrent use of other known nephrotoxic medicine should increase monitoring frequency of renal function.

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.

Patients with inflammatory bowel disease are at risk of developing nephrolithiasis. Cases of nephrolithiasis have been reported during treatment with mesalazine (as contained in **PENTASA® 1 g Suppositories)**. Adequate fluid intake must be ensured during treatment.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with **PENTASA® 1 g Suppositories** (see section 4.8).

Patients with a history of adverse drug reactions to preparations containing sulphasalazine (risk of allergy to salicylates), should be kept under close medical surveillance on commencement of a course of treatment with **PENTASA® 1 g Suppositories**.

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. 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 sign of hypersensitivity, therapy should be discontinued immediately.

If a patient develops dehydration while on treatment with **PENTASA® 1 g Suppositories**, normal electrolyte levels and fluid balance should be restored as soon as possible.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported. Serious blood dyscrasias have been reported very rarely with mesalazine. Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. As stated in the interaction section 4.5, concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving azathioprine, or 6-mercaptopurine or thioguanine. Treatment should be discontinued on suspicion or evidence of these adverse reactions.

PENTASA® 1 g Suppositories should be used with caution in the elderly. Age related factors (such as altered renal and hepatic function as described above and polypharmacy should be taken into consideration) (see section 4.4).

4.5 Interactions with other medicines and other forms of interaction

PENTASA® 1 g Suppositories should not be given with preparations which lower stool pH, e.g. lactulose, and thereby prevent release of the active ingredient.

The concurrent use of other known nephrotoxic agents such as NSAIDs and azathioprine may increase the risk of renal reactions (see 4.4 Special warnings and precautions for use).

In patients who are concomitantly treated with azathioprine, or 6-mercaptopurine, or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine, or thioguanine should be taken into account. Concomitant treatment with **PENTASA® 1 g Suppositories** can increase the risk of blood dyscrasia.

There is weak evidence that **PENTASA® 1 g Suppositories** might decrease the anticoagulant effect of warfarin.

There are no data on interactions between **PENTASA® 1 g Suppositories** and other agents.

4.6 Fertility, pregnancy and lactation

Pregnancy

PENTASA® 1 g Suppositories should be used with caution during pregnancy.

There are no adequate and well-controlled studies of PENTASA use in pregnant women.

Mesalazine is known to cross the placental barrier.

Blood disorders (leucopoenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with **PENTASA® 1 g Suppositories**.

Breastfeeding

PENTASA® 1 g Suppositories should be used with caution during breastfeeding.

Mesalazine is excreted in breast milk. There is limited experience of the use of **PENTASA® 1 g Suppositories** in lactating women.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

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 medicine fever may occasionally occur, and severe cutaneous adverse reactions, including SJS and TEN, have been reported in association with mesalazine treatment (see section 4.4).

Following rectal administration local reactions such as pruritus, rectal discomfort and urge may occur.

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

Common: ≥ 1 % and < 10 %

Rare: ≥ 0,01 % and < 0,1 %

Very rare: < 0,01 %

Nervous system disorders:

Common: Headache

Rare: Dizziness

Very rare: Peripheral neuropathy (including Guillain-Barré syndrome).

Gastrointestinal disorders:

Common: Diarrhoea, abdominal pain, nausea, vomiting, flatulence

Rare: Increased amylase, pancreatitis*.

Very rare: Aggravation of ulcerative colitis, cheilitis and melaena, pancolitis

Skin and subcutaneous tissue disorders:

Common: Rash (including urticaria, erythematous rash).

Rare: Photosensitivity **

Very rare: Reversible alopecia, allergic dermatitis, erythema multiforme

Unknown: Stevens-Johnson Syndrome (SJS) / Toxic epidermal necrolysis (TEN)

Cardiac disorders:

Rare: Myocarditis* and pericarditis*.

Blood and the lymphatic system disorders:

Very rare: Altered blood counts (anaemia, aplastic anaemia, neutropenia, leukopenia (including granulocytopenia), thrombocytopenia, agranulocytosis and pancytopenia), and eosinophilia (as part of an allergic reaction).

Respiratory, thoracic and mediastinal disorders:

Very rare: Allergic alveolitis, allergic and fibrotic lung reactions (including dyspnoea, coughing, bronchospasm), pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis.

Hepato-biliary disorders:

Very rare: Changes in liver function parameters (increase in transaminases and cholestasis parameters (e.g.,

alkaline phosphatase, gammaglutamyl-transferase and bilirubin)); hepatotoxicity (including hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure).

Musculoskeletal, connective tissue and bone disorders:

Very rare: Myalgia, arthralgia, lupus erythematosus-like syndrome (systemic lupus erythematosus).

Renal and urinary disorders ***:

Very rare: Impairment of renal function**** including acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency, urine discolouration.

Immune system disorders

Very rare: Hypersensitivity reaction including anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Reproductive system and breast disorders

Very rare: Oligospermia (reversible)

General disorders and administration site conditions

Common: Anal discomfort and irritation at the application site, pruritus (anal), rectal tenesmus

Very rare: Medicine 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.

(***) Not known: Nephrolithiasis; see section 4.4 for further information

(****) Renal failure has been reported. Mesalazine-induced nephrotoxicity should be suspected in patients

developing renal dysfunction during treatment.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no experience in the overdosage of **PENTASA® 1 g Suppositories**.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 11 Medicines acting on gastrointestinal tract.

Pharmacotherapeutic group: Intestinal anti-inflammatory agents.

ATC code: A07EC Aminosalicylic acid and similar agents

PENTASA® 1 g Suppositories is mesalazine (5-aminosalicylic acid) in a suppository formulation.

The effect of mesalazine after rectal administration is unknown, but appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect.

The therapeutic effect of mesalazine most likely depends on a local contact of the agent with the diseased area

of the intestinal mucosa.

Mesalazine may act through the inhibition of prostaglandin and leukotriene synthesis.

5.2 Pharmacokinetic properties

Administration of **PENTASA® 1 g Suppositories** gives a high concentration of mesalazine in the rectum and a low systemic absorption

Mesalazine is metabolised into N-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.

The absorption following rectal administration is low, but depends on the dose, the formulation and the extent of spreading. Based on urine recovery data in healthy volunteers under steady state conditions given a daily dose of 2 g (1 g x 2) the absorption was approximately 10 %.

Mesalazine and acetyl-mesalazine do not cross the blood-brain barrier, but cross the placenta. Protein binding of mesalazine is 40 – 50 % and of acetyl-mesalazine 70 – 80 %.

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 Excipients

Povidone

Macrogol 6000

Magnesium stearate

Talc

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C, protected from light. Do not refrigerate.

Do not remove from the package until required for use.

6.5 Nature and contents of container

28 Suppositories per carton.

PENTASA® 1 g Suppositories are packed in double aluminium foil blisters, each strip containing 7 suppositories. Four blisters are placed into an outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ferring (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene Ext 30

Pretoria

8. REGISTARTION NUMBER

A40/11/0374

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

9 October 2009

10. DATE OF REVISION OF THE TEXT

22 June 2022

Namibia NS2

Reg No/Nr.: 10/11/0483