1. NAME OF THE MEDICINAL PRODUCT

Pentasa® enema

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pentasa enema bottle contains: 1g mesalazine

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each bottle contains 100ml of a colourless to faint yellow suspension containing 1g mesalazine

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Ulcerative Colitis and Crohn's disease.

4.2 Posology and method of administration

1 enema at bedtime
A visit to the toilet is recommended before administration of enemas and suppositories. Instructions for use appear in the Patient Leaflet.
Shake the enema container well before use. The enema is protected by an aluminum foil bag and should be used immediately after opening.

4.3 Contraindications

Pentasa is contraindicated in:
- patients with known hypersensitivity to salicylates or any of the excipients.
- patients with severe liver and/or renal impairment

4.4 Special warnings and precautions for use

Blood test for differential blood count; liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. 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.
Caution is recommended in patients with impaired hepatic function.
PENTASA should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered, if renal function deteriorates during treatment.
Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment, with Pentasa.

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. Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. Should PENTASA cause 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, the treatment should be discontinued immediately.
If a patient develops dehydration while on treatment with mesalazine, normal electrolyte levels and fluid balance should be restored as soon as possible.
Mesalazine induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely. Treatment should be discontinued on suspicion or evidence of these reactions.
Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine, or thioguanine should be taken into account
There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

Pentasa should be used with caution during pregnancy and lactation and only if the potential benefit outweighs the possible risks in the opinion of the physician.
Pregnancy: Mesalazine is known to cross the placental barrier. There is no adequate data on the use of Pentasa in pregnant women. However, data on limited number of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the fetus/ newborn child. To date no other relevant epidemiologic data are available.
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, embryonic/fetal development, parturition or postnatal development.
Blood disorders (leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA.
PENTASA should only be used during pregnancy if the potential benefit outweighs the possible risk.
Breast-feeding: N-acetyl-5-aminosalicylic acid and to a lesser degree 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 available to date. No controlled studies with PENTASA during breast-feeding have been carried out. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. Therefore, PENTASA should only be used during breast-feeding, if the potential benefit outweighs the possible risk.
If the infant develops diarrhoea, breast-feeding should be discontinued.

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

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

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

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

SOC	**Common ≥1/100 to < 1/10**	**Rare ≥1/10,000 to ≤ 1/1,000**	**Very rare ≤ 1/10,000**	Not known (cannot be estimated from the available data).
Blood and the lymphatic system disorders			Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia thrombocytopenia), and eosinophilia (as part of an allergic reaction),	
Immune system disorders			Hypersensitivity reactions such as allergic exanthema, drug fever lupus erythematosus syndrome, pancolitis	
Nervous system disorders		Headache , dizziness	Peripheral neuropathy	
Cardiac disorders		Myocarditis* Pericarditis*		
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (incl. dyspnoea, cough,	

			bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders		Diarrhoea, abdominal pain, nausea, vomiting increased amylase, flatulence	acute pancreatitis*	
Hepato-biliary disorders			Changes in liver function parameters (increase in transaminases, and cholestasis parameters), hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure	
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Photosensitivity**	Alopecia (Reversible) Erythema multiform	Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN)
Musculoskeletal connective tissue and bone disorders			Myalgia, Arthralgia	
Renal and urinary disorders			impairment of renal function**** (incl. acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency), urine discolouration	Nephrolithiasis***

Reproductive system disorders			Oligospermia (reversible)	

* 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.

*** Renal failure has been reported. Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Acute experience in animals:

Single oral doses of mesalazine of up to 5g/kg in pigs or a single intravenous dose of mesalazine at 920mg/kg in rats were not lethal.

Human experience:

There are rare data on overdosage (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity.

Management of overdose: 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

Pharmacotherapeutic group: Intestinal anti-inflammatory agents

Mechanism of action and pharmacodynamic effects:

Mesalazine is recognised as the active moiety of sulphasalazine in the treatment of ulcerative colitis.It is thought to act locally on the gut wall in inflammatory bowel disease, although its precise mechanism of action has not been fully elucidated.

Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4 and increased free radical formation in the inflamed intestinal tissue are all present in patients with inflammatory bowel disease. Mesalazine has in-vitro and in-vivo pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leukotriene

production and scavenge for free radicals. It is currently unknown which, if any of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

5.2 Pharmacokinetic Properties

General characteristics of the active substance:

Disposition and local availability:

PENTASA enemas are designed to provide the distal part of the intestinal tract with high concentrations of mesalazine and a low systemic absorption. The enemas have been shown to reach and cover the descending colon.

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

Acetyl mesalazine is thought to be clinically as well as toxicologically inactive, although this remains to be confirmed.

Absorption:

The absorption following rectal administration is low, but depends on the dose, the formulation and the extent of spread. Based on urine recoveries in healthy volunteers under steady-state conditions given a daily dose of 2g (1g x 2), about 15-20% of the dose is absorbed after administration of enemas.

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. Both substances are excreted in urine and faeces. The urinary excretion consists mainly of acetyl mesalazine.

Characteristics in patients:

The systematic absorption following administration of PENTASA has been shown to be significantly decreased in patients with active ulcerative colitis compared to those in remission.

In patients with impaired liver and kidney functions, the resultant decrease in the rate of elimination and increased systemic concentration of mesalazine may constitute an increased risk of nephrotoxic adverse reactions.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of excipients

Disodium edetate, sodium metabisulphite, sodium acetate, purified water,

concentrated hydrochloric acid.

6.2 Incompatibilities

Not applicable

6.3 **Shelf Life**

The expiry date of the product is indicated on the packaging materials

6.4 **Storage Conditions**

Store bellow 25°C in the original package, do not freeze.

6.5 **Nature and Contents of Container**

Polyethylene enema bottles fitted with a tip and valve for rectal application, supplied in nitrogen-filled aluminium-foil bags. Presented in cartons containing 7 x 100ml bottles individually foil-wrapped.

7. **License Number**

Pentasa Enema: 137 64 23871

8. **Manufacturer:** Ferring GmbH, Germany

9. **License Holder:** Ferring Pharmaceuticals Ltd

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This leaflet was revised in May 2021 according to MOH guidelines.