1. NAME OF THE MEDICINAL PRODUCT

Pentasa® slow release Tablets, 500 mg

Pentasa® slow release Tablets, 1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Mesalazine
Each Pentasa slow release, 500mg tablet contains: 500 mg mesalazine.
Each Pentasa slow release, 1g tablet contains: 1000 mg mesalazine.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Slow release tablets 500 mg. White-grey to pale-brown, specked round tablets, scored and marked 500mg on one side and 'PENTASA' on the reverse side.
Slow release tablets 1 g.
White-grey to pale-brown, specked oval tablets, and marked with 'PENTASA' on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate ulcerative colitis and Crohn's disease.

4.2 Posology and method of administration

Ulcerative Colitis
Adults:
Active treatment: Individual dosage, up to 4 g mesalazine once daily or in two or three divided doses.

Maintenance treatment: Recommended dosage, 2 g mesalazine once daily.

Crohn's Disease
Adults:
Active treatment: Individual dosage, up to 4 g mesalazine daily in two or three divided doses.

Maintenance treatment: Individual dosage, up to 4 g mesalazine daily in two or three divided doses.

Paediatric population
The safety and efficacy in children below 6 years have not been established.
There is only limited documentation for an effect in children (age 6-18 years)

Ulcerative colitis
Children 6 years of age and older:

Active disease: 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:
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.

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 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 4g/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
Pentasa® Tablets must not be chewed. To facilitate swallowing the tablets may be dispersed in 50ml of cold water. Stir and drink immediately**.** The contents of the sachet should be emptied onto the tongue and washed down with some water or juice.

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 tests (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 liver 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 or the first appearance of signs and symptoms of severe skin reactions, such as skin and rash, mucosal lesions, or any other signs of hypersensitivity, the treatment should be discontinued immediately.

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, or 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 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 a 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 such as 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).

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

SOC	**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, neutropenia, leucopenia pancytopenia, thrombocytopenia,	
Nervous system disorders	Headache , dizziness	Peripheral neuropathy	
Cardiac disorders	Myocarditis* Pericarditis*		
Respiratory, thoracic and mediastinal disorders		allergic and fibrotic lung reactions (incl. dyspnoea, coughing, bronchospasm, alveolitis, pulmonary eosinophilia, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	Diarrhoea, Abdominal pain, Nausea, Vomiting Flatulence	acute pancreatitis	
Renal and urinary disorders		impairment of renal function (incl. acute and chronic interstitial nephritis)*, and renal insufficiency	Nephrolithiasis***

Skin and subcutaneous tissue disorders	Photosensitivity**	Alopecia (Reversible)	Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN)
Musculoskeletal connective tissue and bone disorders		Myalgia, Arthralgia	
Immune system disorders		Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Hepato-biliary disorders		Changes in liver function parameters (increase in transaminases, and cholestasis parameters), hepatitis*, cholestatic hepatitis	
Reproductive system disorders		Oligospermia (reversible)	

* The mechanism of mesalazine induced myocarditis, 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.

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,
ATC Code: A07 EC02

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 tablets consist of ethylcellulose-coated microgranules of mesalazine. Following administration and tablet disintegration the microgranules act as discrete slow-release formulations which allow a continuous release of drug from duodenum to rectum at all enteral pH conditions. The microgranules enter the duodenum within an hour of administration, independent of food co-administration. In healthy volunteers the average small intestinal transit time is approximately 3-4 hours.
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: . Based on urinary 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 approximately 15 minutes following administration. Maximum plasma concentrations are seen 1 - 4 hours post-dose. After a gradual decrease, mesalazine will no longer be 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 500mg x 3 and 2g 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 daily doses of 1.5g, 4g and 6g respectively. For acetyl mesalazine the corresponding concentrations are 6 micromoles/l 13 micromoles/l and 16 micromoles/l respectively.

The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic absorption is reduced.
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 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 urine and faeces. The urinary excretion consists mainly of acetyl mesalazine.
Characteristics in patients:
The delivery of mesalazine to its site of action after oral administration is only slightly affected by pathophysiological changes such as diarrhoea and increased bowel activity observed during active inflammatory bowel disease. A reduction in systemic absorption to 20 – 25% of the daily dose has been observed in patients with accelerated intestinal transit. A corresponding increase in faecal excretion has been seen.
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

Pentasa slow release tablets 500 mg & 1g: Magnesium stearate, talc,

ethylcellulose, povidone, microcrystalline cellulose.

6.2 Shelf Life

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

6.3 Storage Conditions

Store bellow 25°C

6.4 Nature and Contents of Container

Product name	Packaging description	Pack size	

Pentasa slow release tablets 500 mg	Double aluminium foil blisters	10; 20; 50; 100 Tablets	Not all pack sizes may be marketed
Pentasa slow release tablets 1g	Double aluminium foil blisters	60 tablets	

6.5 **Instructions for use/handling**

No special requirements.

6.7 **License Number**

Pentasa slow release tablets 500 mg: 064 73 26905

Pentasa slow release tablets 1g: 147-06-33401-

6.8 **Manufacturer**

Ferring, St-Prex ,Switzerland

6.9 **License Holder**

Ferring Pharmaceuticals Ltd

8, Hashita Street, Industrial Park Caesarea 3088900

ISRAEL

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