1.Trade Name

Pentasa® slow release granules, 1g

Pentasa® slow release granules, 2g

Pentasa® slow release granules, 4g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains: 1g, 2g and 4gr mesalazine respectively.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release granules 1 g
Prolonged release granules 2 g
Prolonged release granules 4 g
White grey to pale white-brown granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Ulcerative Colitis

Adults:

Active disease: 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 disease: 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® Granules must not be chewed.. 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

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

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. In case of acute symptoms of intolerance, i.e. abdominal cramps, 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.
Caution is recommended in patients with impaired liver function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.
The drug is not recommended for use in patients with impaired renal function and in patients with haemorrhagic diathesis. 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 agents, such as NSAIDs and azathioprine, may increase of the risk of renal reactions.
Caution is recommended in patients with active peptic ulcer.
Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment, please refer to section 4.8.
Mesalazine induced cardiac hypersensitivity reactions (myoc- and pericarditis) have been reported rarely. Serious blood dyscrasias have been reported very rarely with mesalazine (see section 4.5). Blood tests for differential blood counts are recommended prior to and during treatment, at the discretion of the treating physician. Treatment should be discontinued on suspicion or evidence of these adverse 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.
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 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 medicinal products and other forms of interaction

No interaction studies have been performed. Combination therapy with Pentasa and azathioprine, 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 the dosage regimen of thiopurine should be adjusted accordingly.
There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

Pentasa should not be used during pregnancy and lactation except when the potential benefits of the treatment outweigh the possible hazards in the opinion of the physician. 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 in the same concentration in umbilical cord and maternal plasma. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. There are no adequate data on the use of Pentasa 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.
Blood disorders (leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with Pentasa slow release granules.
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.
Breast feeding. 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. No controlled studies with Pentasa slow release granules during breast-feeding have been carried out. Only limited experience during lactation in women after oral application is available to date. Hypersensitivity reactions like diarrhoea can not be excluded. If the infant develops diarrhoea, breast-feeding 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

Pentasa slow release granules has no or negligible influence on the ability to drive or use machines

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions seen in clinical trials are diarrhoea, nausea, abdominal pain, headache, vomiting and rash. Hypersensitivity reactions and drug fever may occasionally occur, and 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 (see section 4.4).

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 (anaemia, aplastic anaemia, agranulocytosis, neutropenia, leucopenia (incl. granulocytopenia) pancytopenia thrombocytopenia,and eosinophilia (as part of an allergic reaction).	
Immune system disorders			Hypersensitivity reaction including anaphylactic reaction,	
Nervous system disorders	Headache	dizziness	Peripheral neuropathy Benign intracranial hypertension in adolescents	
Cardiac disorders		Myocarditis* Pericarditis*	Pericardial effusion	
Respiratory, thoracic and mediastinal disorders			Allergic alveolitis, allergic and fibrotic lung reactions (incl. dyspnoea, coughing, bronchospasm, 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			Increased liver enzymes, cholestatis parameters and bilirubin, Hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)	
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Photosensitivity**	Alopecia (Reversible) Quincke's oedema, dermatitis allergic, Erythema multiforme	Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal connective tissue and bone disorders			Myalgia, Arthralgia Lupus erythematosus-like reactions	
Renal and urinary disorders			Renal function impairment (incl. interstitial nephritis*(acute and chronic), nephrotic syndrome, renal insufficiency(acute/chronic), Urine discolouration***	Nephrolithiasis***
Reproductive system 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.
(***) Nephrolithiasis; see section 4.4 for further information

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

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 in rats of 920 mg/kg and a single oral doses of mesalazine in pigs of up to 5g/kg were not lethal.
Human experience:
There is limited clinical experience with overdose of Pentasa which does not indicate renal or hepatic toxicity. Since Pentasa is amino salicylate, symptoms of salicylate toxicity may occur. Symptoms of salicylate over dosage are well described in the literature.
There have been reports of patients taking 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

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, aminosalcylic acid and similar agents
ATC Code: A07 EC02
Mechanism of action and pharmacodynamic effects:
Mesalazine is the active component of sulphasalazine which has been used for a long time in the treatment of ulcerative colitis and Crohn's disease.
The therapeutic value of mesalazine appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mesalazine.
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. The mechanism of action of mesalazine is not fully understood although mechanisms such as activation of the γ-form of peroxisome proliferator-activated receptors (PPAR-γ) and inhibition of nuclear factor-kappa B (NF-κB) in the intestinal mucosa have been implicated. 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.
The risk of colorectal cancer (CRC) is slightly increased in ulcerative colitis. Observed effects of mesalazine in experimental models and patient biopsies support the role of mesalazine in prevention of colitis-associated CRC, with down regulation of both inflammation dependent and non-inflammation dependent signalling pathways involved in the development of colitis-associated CRC. However data from meta-analyses, including both referral and non-referral populations, provide inconsistent

clinical information regarding the benefit of mesalazine in the carcinogenesis risk associated with ulcerative colitis.

5.2 Pharmacokinetic Properties

General Characteristics of the Active Substance
Disposition and local availability:
The therapeutic activity of mesalazine most likely depends on a local contact of the drug with the diseased area of the intestinal mucosa.
Pentasa slow release granules consist of ethylcellulose coated microgranules of mesalazine. The coated microgranules enter the duodenum within an hour of administration, independent of food co-administration. Mesalazine is continuously released from the coated microgranules throughout the gastrointestinal tract in any enteral pH conditions.
Absorption: Bioavailability of Pentasa after oral administration can be estimated to approx.. 30%, based on urine recovery data in healthy volunteers. Maximum plasma concentrations are seen 1-6 hours post-dose. A once-daily dosing regimen of mesalazine (1 × 4 g/d) and a twice-daily dosage (2 × 2 g/d) results in a comparable systemic exposure (AUC) over 24 hours and indicate a continuous release of mesalazine from the formulation over the treatment period. Steady-state is reached after a treatment period of 5 days following oral administration.

	Single dose		Steady state	
Mesalazine	Cmax (ng/mL)	AUC 0-24 (h·ng/mL)	Cmax (ng/mL)	AUC 0-24 (h·ng/mL)
2 g BID	5103.51	36,456	6803.70	57,519
4 g OD	8561.36	35,657	9742.51	50,742
Molecular weight of mesalazine: 153.13 g/moL; Ac-mesalazine: 195.17 g/moL.				

The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic exposure may be increased.
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%.
Metabolism: Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl-mesalazine (acetyl-mesalazine) principally by NAT-1. Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient. 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×3 and 2 g×3, respectively, implying a dose-dependent acetylation which may be subject to saturation.
Elimination: Due to continuous release of mesalazine throughout the gastrointestinal tract, the elimination half-life cannot be determined after oral administration. However, once the formulation is not present in the GI tract elimination will follow the plasma half-life of orally or IV administered uncoated mesalazine, which is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes.
Characteristics in patients:
Pathophysiologic changes such as diarrhoea and increased bowel acidity observed during active inflammatory bowel disease have only a minor impact on the delivery of mesalazine to the intestinal mucosa after oral administration. A urine excretion 20-

25% of the daily dose has been observed in patients with accelerated intestinal transit. Likewise, a corresponding increase in faecal excretion has been seen.

5.3 Preclinical Safety Data

Toxic renal effects have been demonstrated in all species tested. Rat and monkey dosages and plasma concentrations at the No Observed Adverse Effect Levels (NOAELs) exceed those used in humans by a factor of 2-7.2.
In vitro test systems and in-vivo studies showed no evidence of mutagenic effects.
Studies on the tumourigenic potential carried out in rats showed no evidence of any substance-related increase in the incidence of tumours.
Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pentasa® slow release granules 1g; 2g; 4 g

Ethylcellulose, Povidone.

6.2 Incompatibilities: None applicable

6.3 Shelf Life: The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage: Store bellow 25°C in the original package, protect from light.

6.5 Nature and Contents of Container

Pentasa® slow release granules 1g, 2g and 4 g

Polyester/Aluminium/LD polyethylene sachet.

6.6 Special precautions for disposal and other handling

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

6.7 License Number

Pentasa® slow release granules 1g: 114 57 29591

Pentasa® slow release granules 2g: 138 91 31560

Pentasa® slow release granules 4g: 157-47-34816

6.8 Manufacturer

Ferring, St-Prex ,Switzerland

6.9 License Holder

Ferring Pharmaceuticals Ltd

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