Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pentasa Sachet 4 g Prolonged-release granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains mesalazine 4 g
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release granules
White-grey to pale white-brown granules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate ulcerative colitis.

4.2 Posology and method of administration

Posology
Ulcerative colitis

Adults
Active disease
Individual dosage, up to 4 g mesalazine once daily or divided into 2-4 doses.
Maintenance treatment
Individual dosage. Recommended dosage, 2 g mesalazine once daily.

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

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.

Method of administration
Oral use

The granules must not be chewed.
The contents of the sachet should be emptied onto the tongue and washed down with some water or orange juice. Alternatively the entrie content of the sachet can be taken with yogurt and consumed immediately.

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 regularly monitored (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 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 (myo- 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 is 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.

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 hypertension occurs, discontinuation of mesalazine should be considered.

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 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 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 Sachet 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 at similar concentrations in umbilical cord and

maternal plasma. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development. There are no adequate and well controlled studies of Pentasa 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.
Blood disorders (leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with Pentasa Sachet.

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 Sachet 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 cannot 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 Sachet 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 fevermay 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, leukopenia (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 Idiopathic intracranial hypertension (see section 4.4)	
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	Acute pancreatitis* Increased amylase (blood and/or urine)	Pancolitis	
Hepato-biliary disorders			Increased liver enzymes, cholestasis parameters and bilirubin, hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)	
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Photosensitivity**	(Reversible) alopecia Quincke's oedema, dermatitis allergic, Erythema multiforme	Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue			Myalgia	

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)
disorders			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 and breast 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.

(***) 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 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Acute experience in animals: A single intravenous dose of mesalazine in rats of 920 mg/kg and single oral doses of mesalazine in pigs up to 5 g/kg were not lethal.

Human experience: There is limited clinical experience with overdose of Pentasa sachet which does not indicate renal or hepatic toxicity. Since Pentasa is an 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 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

Pharmacotherapeutic groups: Intestinal anti-inflammatory agents, aminosalicylic acid and similar agents
ATC code: A07E C02

Mesalazine is the active component of sulfasalazine, 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 leukocyte 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 leukocyte 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 Sachet prolonged 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**	
	Cmax (ng/mL)	**AUC 0-24 (h·ng/mL)**	**Cmax (ng/mL)**	**AUC 0-24 (h·ng/mL)**
Mesalazine				
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 the 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 diseasehave 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

Ethylcellulose
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
The granules should be used immediately after first opening of the sachet.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyester/Aluminium/LD polyethylene sachet.

Pack sizes: 1 x 20, 1 x 30, 1 x 50, 1 x 100 sachets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd
United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1009/006/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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