Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pentasa 1g Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains mesalazine 1g.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository
White to tan, spotted, oblong suppository.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of ulcerative proctitis.

4.2 Posology and method of administration

Adults:
Active treatment:
1 g mesalazine twice daily for two to four weeks.

Maintenance treatment:
1-2 g mesalazine daily.

Paediatric population:
There is little experience with only limited documentation for an effect in children.

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

Most patients who are intolerant or hypersensitive to sulphasalazine are able to take Pentasa without risk of similar reactions. However, caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy 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 renal impairment. 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 should increase monitoring frequency of renal function.

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.

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 (myocarditis and pericarditis) have been reported rarely.Serious blood dyscrasias have been reported veryrarely 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.

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.

Severe cutaneous adverse reactions
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.
Pentasa should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

Combination therapy with Pentasa and azathioprine, or 6-mercaptopurine or thioguanine have in several studies shown a higher frequency of myelosuppressive effects, and an interaction seems to exist, however, the mechanism behind the interaction is not fully established. Regular monitoring of white blood cells is recommended and dosage regime of thiopurines 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 be used with caution during pregnancy and lactation and only if the potential benefit outweighs 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 (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with Pentasa.

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.

Breastfeeding: 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. No controlled studies with Pentasa during breast-feeding have been carried out.

Hypersensitivity reactions like diarrhoea in the infant 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.
Oligospermia (reversible) has been reported after use of mesalazine, see section 4.8.

4.7 Effects on ability to drive and use machines

Treatment with Pentasa is unlikely to affect the ability to drive and/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.

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

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 (including 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	
Cardiac disorders		Myocarditis* Pericarditis*		
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (incl. dyspnoea, coughing, bronchospasm, allergic alveolitis), pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis	
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Vomiting Flatulence	Increased amylase, acute pancreatitis*	Pancolitis	
Hepato-biliary disorders			Increase in transaminases, increase in cholestasis parameters (e.g. alkaline phosphatase, gamma-glutamyltransferase and bilirubin), hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)	
Skin and subcutaneous	Rash (incl. urticaria,	Photosensitivity **	Alopecia reversible, dermatitis allergic, erythema multiform	Stevens-Johnson syndrome

tissue disorders	erythematous rash)			(SJS), toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders			Myalgia, Arthralgia, Lupus erythematosus-like syndrome (systemic lupus erythematosus)	
Renal and urinary disorders			Renal function impairment (incl. acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency),	Nephrolithiasis§ Urine discolouration§
Reproductive system disorders			Oligospermia (reversible)	
General disorders and administration site conditions	Anal discomfort and irritation at the application site, pruritus (anal), rectal tenesmus		Drug Fever	

(*)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.

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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

Human experience:
There is limited clinical experience with overdose of Pentasa which does not indicate renal or hepatic toxicity. But since Pentasa is an amino salicylate, symptoms of salicylate toxicity such as acid-base balance disorder, hyperventilation, pulmonary oedema, vomiting, dehydration and hypoglycaemia 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 the management of overdose is supportive and symptomatic. The treatment at the 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:
It has been established that mesalazine is the active component of sulphasalazine which is used for the treatment of ulcerative colitis and Crohn's disease. Based on clinical results, the therapeutic value of mesalazine after oral as well as rectal administration 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 has 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.

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 suppositories and rectal suspensions are designed to provide the distal part of the intestinal tract with high concentrations of mesalazine and a low systematic absorption. Suppositories cover the rectum, whereas rectal suspensions have been shown to reach and cover the descending colon.

Absorption:
The absorption following rectal administration is low, and 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 2 g (1 g x 2), approximately 10% of the dose is adsorbed after administration of suppositories whereas about 15-20% is absorbed after administration of rectal suspensions.

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 from Pentasa 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 activity observed during active inflammatory bowel disease has 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.
No significant toxicity associated with the gastrointestinal tract, liver or haematopoietic system in animals has been observed.

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.

Mesalazine is deemed not to pose a risk to the environment at the doses prescribed for use in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Macrogol 6000
Magnesium stearate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Each suppository is individually packed in double aluminium foil and presented in cartons of 28 suppositories.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special 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

PA1009/006/002

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