Pentasa Slow Release Tablets 1g

Summary of Product Characteristics Updated 03-Jul-2014 | Ferring Pharmaceuticals Ltd

1. Name of the medicinal product

PENTASA® Slow Release Tablets 1g

2. Qualitative and quantitative composition

Each tablet contains mesalazine 1g

3. Pharmaceutical form

Tablet

White-grey to pale-brown, specked oval tablets, and marked with 'PENTASA' on both sides.

4. Clinical particulars

4.1 Therapeutic indications

PENTASA Slow Release Tablets 1g are indicated for the treatment of mild to moderate exacerbations of ulcerative colitis. For the maintenance of remission of ulcerative colitis.

4.2 Posology and method of administration

Ulcerative Colitis

The tablets must not be crushed or chewed. They may be swallowed whole or broken up. To facilitate swallowing they may be dispersed in 50ml of cold water. Stir and drink immediately.

Adults:

Acute treatment: Individual dosage of up to 4g mesalazine once daily or in two or three divided doses.

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

Children:

Not recommended.

Elderly Patients:

The usual adult dose applies.

Route of administration: oral.

4.3 Contraindications

PENTASA is contraindicated in:

- patients with known sensitivity to salicylates
- children under the age of 15 years
- patients with severe liver and/or renal impairment
- patients allergic to any of the ingredients

4.4 Special warnings and precautions for use

Serious blood dyscrasias have been reported rarely with mesalazine. Haematological investigations should be performed if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.

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). Caution is recommended in patients with impaired liver function.

It is recommended that mesalazine is used with extreme caution in patients with mild to moderate renal impairment (see section 4.3).

Patients on any oral formulation of mesalazine should have renal function monitored, with serum creatinine levels measured prior to treatment start, every 3 months for the first year, then 6 monthly for the next 4 years and annually thereafter. Treatment with mesalazine should be discontinued if renal function deteriorates.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent use of mesalazine with other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions (see section 4.4).

Concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving azathioprine or 6-mercaptopurine.

4.6 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.

Mesalazine is known to cross the placental barrier, but the limited data available on its use in pregnant women do not allow assessment of possible adverse effects. No teratogenic effects have been observed in animal studies.

Blood disorders (leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA.

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 cannot be excluded.

4.7 Effects on ability to drive and use machines

No adverse effects.

4.8 Undesirable effects

Mesalazine may be associated with an exacerbation of the symptoms of colitis in those patients who have previously had such problems with sulphasalazine.

Undesirable effects are as follows:

Common	*Gastrointestinal disorders:*
(≥1% and <10%)	Nausea, vomiting, diarrhoea, abdominal pain
	Skin disorders:
	Rash (including urticaria and erythematous rash)
	General:
	Headache
Rare	*Blood disorders:*
(≥0.01% and < 0.1%)	Leucopenia (including granulocytopenia), neutropenia, agranulocytosis, aplastic anaemia, thrombocytopenia
	Nervous system disorders:
	Peripheral neuropathy
	Cardiac disorders:
	Myocarditis, pericarditis
	Respiratory disorders:

	Allergic lung reactions (including dyspnoea, coughing, allergic alveolitis, pulmonary eosinophilia, pulmonary infiltration, pneumonitis)
	Gastrointestinal disorders:
	Pancreatitis, increased amylase
	Liver:
	Abnormalities of hepatic function and hepatotoxicity (including hepatitis, cirrhosis, hepatic failure)
	Urogenital:
	Abnormal renal function (including interstitial nephritis, nephrotic syndrome), urine discolouration (*see additional text)
	Collagen disorders:
	Lupus erythematosus-like reactions
Very rare	*Blood disorders:*
(<0.01%)	Anaemia, eosinophilia (as part of an allergic reaction) and pancytopenia
	Liver:
	Increased liver enzymes and bilirubin
	Skin disorders:
	Reversible alopecia, bullous skin reactions including erythema multiforme and Stevens-Johnson syndrome
	Musculo-skeletal disorders:
	Myalgia, arthralgia
	Allergic reactions:
	Hypersensitivity reactions, drug fever.

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

The mechanism of mesalazine induced myocarditis, pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

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:

No cases of overdose have been reported.

Management of overdose in man:

Symptomatic treatment at hospital. Close monitoring of renal function. Intravenous infusion of electrolytes may be used to promote diuresis.

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 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 urine 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 continuous release of mesalazine from PENTASA 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

Povidone

Ethylcellulose

Magnesium stearate

Talc

Microcrystalline cellulose

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Blister: Double aluminium foil

Pack size: 60 Tablets

6.6 Special precautions for disposal and other handling

None

Administrative data

7. Marketing authorisation holder

Ferring Pharmaceuticals Ltd.

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United Kingdom

8. Marketing authorisation number(s)

PL 3194/0108

9. Date of first authorisation/renewal of the authorisation

02/09/2011

10. Date of revision of the text

May 2014

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