IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1500/049/001
Case No: 2083450

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Profind Wholesale Ltd.

Unit 625, Kilshane Avenue, **Northwest Business Park**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Pentasa 500mg Prolonged-release Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/07/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pentasa 500mg Prolonged-release Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains mesalazine 500 mg.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Product imported from Italy:
White-grey to pale brown, speckled, round, prolonged release tablets, scored and marked '500mg' on one side and 'PENTASA' on the reverse side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of Ulcerative colitis and Crohn’s disease.

4.2 Posology and method of administration

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

Maintenance treatment: Recommended dosage, 2g once daily.

Children:
Individual dosage, recommended starting dose is 20-30mg/kg bodyweight daily in two or three divided doses.

Crohn's Disease
Adults***:***
Acute Treatment: Individual dosage of up to 4g mesalazine daily in two or three divided doses.

Maintenance treatment: Individual dosage, recommended starting dose is 1500 mg mesalazine daily in two or three divided doses.

Children:
Individual dosage, recommended starting dose is 20-30 mg/kg bodyweight daily in two or three divided doses.

4.3 Contraindications

1. Use in patients hypersensitive to salicylates
2. Use in children under the age of 2 years
3. Use in patients with active peptic ulcer
4. Use in patients with coagulopathy
5. Use in patients with severe liver and/or renal impairment
6. 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 be used with extreme caution in patients with mild to moderate renal impairment. (*See section 4.3, Contraindications*).

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 nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

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, Special warnings and precautions for use*)

4.6 Pregnancy and lactation

Experience of use during pregnancy is limited. 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.

Mesalazine is excreted in breast milk. The concentration is lower than in maternal blood, whereas the metabolite, acetyl mesalazine appears in similar or increased concentrations. No adverse effects in suckling babies of mothers treated with Pentasa have been reported, but the data are very limited.

4.7 Effects on ability to drive and use machines

No adverse effects.

4.8 Undesirable effects

The most frequent adverse reactions seen in clinical trials are diarrhoea (3%), Nausea (3%), abdominal pain (3%), headache (3%), vomiting (1%) and rash (1%). Hypersensitivity reactions and drug fever may occasionally occur.

SOC	**Common ≥1/100 to ≤1/10**	**Rare ≥1/10,000 to ≤ 1/1,000**	**Very rare ≤1/10, 000**
Blood and the lymphatic system disorders			Esoinophilia (as part of an allergic reaction) Anaemia Aplastic anaemia Leukopenia (incl. granulocytopenia) Thromboctopenia Agranulocytosis Pancytopenia
Nervous System Disorders	Headache		Peripheral neuropathy
Cardiac disorders		Mycocarditis* Pericarditis*	
Respiratory, thoracic and mediastinal disorders			Allergic lung reactions (incl. dyspnoea, coughing, allergic alveolitis, pulmonary eosinophilia, pulmonary infiltration, pneumonitis)
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Vomiting	Increased amylase, pancreatitis*	
Hepato-biliary disorders			Increased liver enzymes and bilirubin, hepatotoxicity (incl. hepatitis*, cirrhosis, hepatic failure)
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, Erythematous rash)		Reversible alopecia Bullous skin reactions including erythema multiforme and Stevens Johnson Syndrome
Musculoskeletal, connective tissue and bone disorders			Myalgia Arthralgia Isolated reports of lupus erythematosus-like reactions

Renal and urinary disorders			Abnormal renal function (incl. interstitial nephritis*, nephrotic syndrome, urine discolouration

*The mechanism of mesalazine induced myocarditis, pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin. It is important to note that several of these disorders can also be attributed to be the inflammatory bowel disease itself.

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 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 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

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

A cardboard carton containing ten aluminium foil blisters (10 tablets per blister).
Pack size : 100 tablets

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 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/49/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th June 2010

10 DATE OF REVISION OF THE TEXT

July 2010