PACKAGE INSERT FOR PENTASA® 1 g ENEMA

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

PENTASA® 1 g ENEMA

COMPOSITION

Each 100 ml rectal suspension contains 1 g mesalazine and the following excipients: disodium edetate & sodium metabisulphite as antioxidants; sodium acetate, purified water and hydrochloric acid for pH adjustment.

PHARMACOLOGICAL CLASSIFICATION

A. 11 Medicines acting on gastrointestinal tract.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The exact mode of action of mesalazine after rectal administration is unknown, but appears to be due to a local effect on the inflamed intestinal tissue, rather than to a systemic effect.
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 (IBD). Mesalazine has *in vitro* and *in vivo* pharmacological effects that inhibit leukocyte chemotaxis, decrease cytokine and leukotriene production, and scavenge for free radicals.

Pharmacokinetic properties

Biotransformation:

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl-mesalazine (acetyl-mesalazine). Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient.

Acetyl-mesalazine is thought to be [clinically and toxicologically] inactive.

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 absorbed after administration of suppositories whereas about 15 - 20 % is absorbed after administration of enemas.

Distribution:

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.

Both mesalazine and acetyl-mesalazine are excreted with the urine and faeces.

The urinary excretion consists mainly of acetyl-mesalazine.

Clinical Trials

287 patients were enrolled into an 8 week randomised, double-blind, placebo-controlled study investigating the efficacy and safety of Pentasa® enemas. Patients with acute distal ulcerative colitis, specifically proctosigmoiditis or proctitis, were randomised to receive a 100 ml mesalazine enema of either 1 g, 2 g or 4 g or placebo, at bedtime. Three primary efficacy variables were assessed; Physicians Global Assessment, Treatment Failure, and Sigmoidoscopic Index (using a

15 point scale). See below table.

Table 1: Primary Efficacy Variables. (Intent-to-treat)

	Placebo	1 g mesalazine	2 g mesalazine	4 g mesalazine
Physicians Global Assessment: Complete relief of symptoms or marked improvement % (n)	27 % (19)	67 % (49)*	65 % (46)*	75 % (55)*
Treatment failure % (n)	37 % (26)	8 % (6)*	11 % (8)†	10 % (7)*
Sigmoidoscopic Index:	n=70	n=73	n=71	n=73
Baseline Mean (SE)	10,5 (0,33)	9,9 (0,29)	10,6 (0,25)	10,4 (0,30)
Last visit Mean (SE)	8,6 (0,58)	4,2 (0,46)	4,5 (0,57)	3,9 (0,50)
Change: Mean (SE)	-1,8 (0,51)	-5,8 (0,50) *	-5,9 (0,50)*	-6,4 (0,50)*

*Pentasa vs. placebo $p<0.0001$

†Pentasa vs. placebo $p=0.0002$

All 3 doses of mesalazine were statistically significantly better than placebo. A flat dose response relationship was demonstrated above 1 g.

INDICATIONS

PENTASA® 1 g ENEMA is indicated for the treatment of ulcerative proctosigmoiditis and left-sided colitis.

CONTRAINDICATIONS

- Hypersensitivity to any of the components of **PENTASA® 1 g ENEMA** and salicylates.
- Severe liver and/or renal impairment.

WARNINGS AND SPECIAL PRECAUTIONS

Caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates).

Caution is recommended in patients with impaired liver function. Liver function parameters such as ALT or AST should be assessed prior to and during treatment, at regular intervals.

PENTASA® 1 g ENEMA 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. 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.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported.

*S*erious blood dyscrasias have been reported with **PENTASA® 1 g ENEMA**. Blood test for differential blood count is recommended prior to and during treatment, at regular intervals.

Concomitant treatment with **PENTASA® 1 g ENEMA** can increase the risk of blood dyscrasia in patients receiving azathioprine or 6-mercaptopurine (see INTERACTIONS). **PENTASA® 1 g ENEMA** treatment should be discontinued on suspicion or evidence of these adverse reactions.

PENTASA® 1 g ENEMA should be inserted into the rectum. It should not be taken by mouth.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

It is unknown if treatment with **PENTASA® 1 g ENEMA** affects the ability to drive and/or use machines.

INTERACTIONS

Combination therapy with **PENTASA® 1 g ENEMA** and azathioprine or 6-mercaptopurine have shown a higher frequency of leucopenia, and an interaction seems to exist. Regular monitoring of white blood cells is recommended and the dosage requirements of thiopurines should be adjusted accordingly.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. Hypersensitivity reactions to mesalazine in breast milk, like diarrhoea, have been reported in the suckling infant.

Mesalazine is known to cross the placental barrier and its concentration in umbilical cord plasma is one tenth of the concentration in maternal plasma. The metabolite acetyl-mesalazine is found in the same concentration in umbilical cord and maternal plasma. Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in newborns of mothers being treated with **PENTASA® 1 g ENEMA.**

Women receiving **PENTASA® 1g ENEMA** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

PENTASA® 1 g ENEMA should be inserted into the rectum. It should not be taken by mouth.

Ulcerative proctosigmoiditis and left-sided colitis:

One enema should be administered at bedtime.

A visit to the toilet is recommended before administration.

Shake the enema container well before use. The enema is protected by an aluminium foil bag and should be used immediately after opening the bag.

See separate instructions for use in the enclosed Patient Information Leaflet.

SIDE EFFECTS

The most frequent adverse reactions seen in clinical trials were 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 faecal urge may occur.

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance:

MedDRA Organ Class	**Common (1 - 10 %)**	**Rare (0,01 - 0,1 %)**	**Very rare (<0,01 %)**	**Post marketing- (frequency unknown)**
Blood and the lymphatic system disorders			eosinophilia (as part of an allergic reaction), anaemia, aplastic anaemia, leucopenia (incl. granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, pancytopenia	
Immune system disorders				Hyper-sensitivity reaction, anaphylaxis
Nervous system disorders	Headache		peripheral neuropathy	
Cardiac disorders		Myocarditis* and pericarditis*		

Respiratory, thoracic and mediastenal disorders			Allergic and fibrotic lung reactions (incl. dyspnoea, coughing, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	diarrhoea, abdominal pain, nausea, vomiting	increased amylase, pancreatitis*, flatulence		
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, lupus erythematosus-like reactions	
Musculo-skeletal,			myalgia, arthralgia	

connective tissue and bone disorders				
Renal and urinary disorders			Renal function impairment (incl. interstitial nephritis*, nephrotic syndrome, renal insufficiency) urine discolouration	
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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment is symptomatic and supportive in a hospital. Close monitoring of renal function is advised.

IDENTIFICATION

White to slightly yellow suspension.

PRESENTATION

Clear, translucent LDPE bottles containing 100 ml suspension, with valve tips for rectal application.

Each bottle is supplied in a nitrogen filled EPT/ALU/LDPE-foil bag.

7 bottles containing 100 ml suspension (each in a nitrogen filled EPT/ALU/LDPE-foil bag) are packed into an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light. Do not freeze.

Do not remove from the foil bag and outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

44/11/0888

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ferring (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene Ext 30

Pretoria

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Registration date: 02 October 2014.

Revision date: 09 January 2015.