AUSTRALIAN PRODUCT INFORMATION – PENTASA® (MESALAZINE) ENEMAS AND SUPPOSITORIES

1 NAME OF THE MEDICINE
Mesalazine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
PENTASA Enemas contain mesalazine 1g/100mL as the active ingredient as well as the following inactive excipients: disodium edetate, sodium metabisulphite, sodium acetate, purified water, hydrochloric acid to pH 4.8.

PENTASA Suppositories contain 1 g mesalazine as the active ingredient as well as the following inactive excipients: magnesium stearate, purified talc, povidone and macrogol 6000.

3 PHARMACEUTICAL FORM
Enema 1 g
Suppositories 1 g

Appearance of PENTASA Enema 1 g: White to slightly yellow suspension with a pH value between 4.4 and 5.0.

Appearance of PENTASA suppositories 1 g: White to tan, spotted, oblong suppositories.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Enemas: Treatment of ulcerative proctosigmoiditis and/or treatment of left-sided ulcerative colitis.

Suppositories: Treatment of ulcerative proctitis.

4.2 DOSE AND METHOD OF ADMINISTRATION
A visit to the toilet is recommended before administration of enemas and suppositories.

Enemas: The contents of one (1 g) enema inserted into the rectum at bedtime. Shake the enema container well. The enema should be used not more than 5 minutes after being shaken.

Suppositories: One (1 g) suppository once daily.

4.3 CONTRAINDICATIONS
Hypersensitivity to mesalazine or any other component of the product or salicylates.
Severe liver or renal impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Most patients who are intolerant or hypersensitive to sulfasalazine are able to take PENTASA without the risk of similar reactions. However, caution is recommended when treating patients allergic to sulfasalazine because of the risk of allergy to salicylates (also see SECTION 4.3 CONTRAINDICATIONS).

Of 287 patients participating in a clinical study, 44 were known to be allergic to sulfasalazine. Whilst only 3 of these patients subsequently exhibited symptoms that may be associated with hypersensitivity to mesalazine, caution should be exercised when initiating treatment of patients with a history of hypersensitivity to

sulfasalazine. Treatment should be discontinued in the event of symptoms suggestive of hypersensitivity such as rash, fever, nausea, headache, abdominal discomfort or pain or exacerbation of diarrhoea.

PENTASA Enemas contain sodium metabisulphite and should be used with caution, particularly in patients with asthma as they may cause hypersensitivity reactions such as anaphylactic reactions or asthmatic episodes.

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 (also see SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Also, blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. As stated in SECTION 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, 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 (also see SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Mesalazine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely.
Pentasa Enema may colour the linen and toilet.

Use in hepatic impairment

Caution is recommended in patients with impaired liver function (also see SECTION 4.3 CONTRAINDICATIONS). Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.

Use in renal impairment

Mesalazine is not recommended for use in patients with renal impairment (see also SECTION 4.3 CONTRAINDICATIONS). Renal function should be monitored regularly in all patients (e.g. serum creatinine, urinalysis for protein) 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.

Use in the elderly

Age related factors (such as altered renal and hepatic function as described above and polypharmacy) should be taken into consideration.

Paediatric use

PENTASA should not be used in children 12 years of age and under, as there is limited experience with this age group.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Whilst there are no data on interactions between PENTASA and other drugs, in common with other salicylates, interactions may occur during concomitant administration of mesalazine and the following drugs:

- Coumarin type anticoagulants (e.g. warfarin sodium) – possible potentiation of the anticoagulant effect (increasing the risk of gastrointestinal haemorrhage)
- Glucocorticoids – possible increase in undesirable gastric effects
- Sulfonylureas – possible increase in the blood glucose lowering effects
- Methotrexate – possible increase in toxic potential of methotrexate
- Probenecid or sulfinpyrazone – possible attenuation of the uricosuric effects
- Spironolactone or frusemide – possible attenuation of the diuretic effects
- Rifampicin – possible attenuation of the tuberculostatic effects.

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.

The concomitant use of mesalazine with other known nephrotoxic agents, such as NSAIDS and azathioprine, may increase the risk of renal reactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Oral administration of mesalazine at doses up to 400 mg/kg/day to male rats prior to mating and female rats from prior to mating through gestation and lactation did not affect fertility or elicit embryofetal toxicity.

Use in Pregnancy

(Category C)
Oral administration of mesalazine during organogenesis in rats and rabbits at respective doses up to 1000 and 800 mg/kg/day was associated with concomitant embryofetal toxicity and maternotoxicity. At a dose of 1000 mg/kg/day in rats, fetuses showed enlarged brain ventricles. Non-embryofetal toxic and non-maternotoxic dosages were 500 and 400 mg/kg/day in rats and rabbits, respectively.

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. 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 newborns of mothers being treated with PENTASA.

Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with non-steroidal anti-inflammatory drugs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Data on 165 women exposed to mesalazine during pregnancy were prospectively collected and pregnancy outcome was compared with that of a control group. The investigators concluded that mesalazine does not represent a major teratogenic risk, as the reported rate of major malformations was within the expected baseline risk of the general population.

PENTASA should be used with caution during pregnancy only if the potential benefits outweigh the possible hazards in the opinion of the physician. The underlying condition itself (inflammatory bowel disease/IBD) may increase risks for the pregnancy outcome.

Use in Lactation

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.

In rats, oral administration of mesalazine during late gestation and lactation at doses of 400 and 800 mg/kg/day was associated with maternotoxicity and toxicity in offspring; a dose of 200 mg/kg/day was devoid of toxicity in either generation. Blood disorders (leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA.

There is limited experience of the use of oral mesalazine in lactating women. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. PENTASA should be used with caution during lactation and only if the potential benefits outweigh the possible hazards in the opinion of the physician.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following table (Table 1.) lists treatment related Adverse Reactions (of a frequency of ≥ 1%) from a 287 patient clinical study investigating the efficacy and safety of three doses of PENTASA Enema in the treatment of acute exacerbations of Ulcerative Proctosigmoiditis. There did not appear to be any dose relationship to the frequency of adverse events.

Table 1.

Adverse Reaction	PENTASA n=217* n (%)	Placebo n=70 n (%)
Gastrointestinal		
Diarrhoea	5 (2.3%)	3 (4.3%)
Nausea	4 (1.8%)	2 (2.9%)
Flatulence	3 (1.4%)	1 (1.4%)
Rectal Distension	3 (1.4%)	0
Colitis Ulcer (Proctitis Ulcer)	1 (0.5%)	1 (1.4%)
Glossitis	1 (0.5%)	0
Melena	0	1 (1.4%)
Nausea Vomit	0	1 (1.4%)
General		
Pain Abdomen	7 (3.2%)	2 (2.9%)
Headache	3 (1.4%)	2 (2.9%)
Pain (Pain Back)	2 (0.9%)	1 (1.4%)
Dermatological		
Alopecia	3 (1.4%)	0
Rash (Mac Pap/Vesic Bull)	3 (1.4%)	0
Other		
Conjunctivitis	1 (0.5%)	1 (1.4%)
Total Patients: n (%)**	30 (13.8%)	7 (10.0%)

*Includes all patients for three PENTASA dose groups, 1 g/100mL, 2 g/100 mL & 4 g/100 mL.
**Some patients experienced more than one event.

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

The following table (Table 2.) represents the frequency of adverse effects based on clinical trials and reports from post-marketing surveillance for all formulations of PENTASA, including rectals:

Table 2.

MedDRA Organ Class	**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			Altered blood counts such as: anaemia, aplastic anaemia, agranulocytosis, neutropenia, leukopenia (including granulocytopenia), pancytopenia, thrombocytopenia and eosinophilia (as part of an allergic reaction)
Immune system disorders			Hypersensitivity reaction, anaphylactic reaction Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and erythema multiforme.
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy
Cardiac disorders		Myo*- and pericarditis*	
Respiratory, thoracic and mediastenal disorders			Allergic and fibrotic lung reactions (including 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 transaminase, increase in cholestasis parameters (e.g. alkaline phosphatase, gamma glutamyltransferase and bilirubin), hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Photosensitivity**	Alopecia reversible, dermatitis allergic, Stevens-Johnson Syndrome (SJS)
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, urine discolouration
Reproductive system disorders			Oligospermia (reversible)
General disorders and administration site conditions	Only relevant to rectal dosage forms of PENTASA: anal discomfort and irritation at the application site, pruritus, tenesmus		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

It is important to note that several of these disorders can also be attributed to the inflammatory process itself.

Hypersensitivity reactions and drug fever may occasionally occur. Mesalazine may be associated with an exacerbation of the symptoms of colitis in those patients who have previously had such problems with sulfasalazine.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute experience in animals: Single oral doses of mesalazine 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. But since PENTASA is an amino salicylate, symptoms of salicylate toxicity may occur. Symptoms of mild salicylate intoxication include nausea, vomiting, tinnitus or dizziness. Symptoms of more severe salicylate intoxication include hyperthermia, dehydration, disturbance of electrolyte balance and blood pH, seizures, dysrhythmias, coagulopathy, renal failure and coma.

There have been reports of patients taking daily doses of 8 g for a month without any adverse events.

Management of overdose in humans: There is no specific antidote. As PENTASA is an aminosalicylate, conventional therapy for salicylate toxicity may be beneficial. General supportive and symptomatic measures are recommended. Steps to prevent further gastrointestinal tract absorption may be appropriate. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Renal function should be closely monitored.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Intestinal anti-inflammatory agents (A07 EC02).

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

It has been established that mesalazine is the active component of sulfasalazine, which is used for the treatment of ulcerative colitis and large bowel Crohn's disease. Based on clinical results, the therapeutic value of mesalazine after oral as well as rectal administration appears to be due to a local effect on the inflamed intestinal tissue, rather than to systemic effects. There is information suggesting that the 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 mechanisms of action of mesalazine are 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* pharmacological effects that inhibit leukocyte chemotaxis, decrease cytokine production, scavenge for free radicals and also reduce leukotriene production via inhibition of the lipo-oxygenase pathway. Prostaglandin production is reduced via inhibition of the cyclo-oxygenase pathway. It is currently unknown which, if any, of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

Clinical trials

PENTASA Enemas

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 proctosigmoiditits 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; Physical Global Assessment, Treatment Failure, and Sigmoidoscopic Index (using a 15 point scale). See Table 3.

Table 3: 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.

PENTASA Suppositories

50 patients with active mild to moderate ulcerative proctitis were enrolled into a 2 week double-blind, placebo-controlled study investigating the efficacy of daily application of PENTASA suppositories in the treatment of ulcerative proctitis. Patients were randomised to receive either placebo or PENTASA 1 g Suppositories. The primary endpoint was endoscopic remission (score of 0-1 on a scale of 0-5) at 2 weeks and the secondary endpoint was clinical remission (<4 bowel movements daily and absence of other clinical symptoms).

Table 4: Primary & Secondary Endpoints

	Placebo n=24	PENTASA n=26
Endoscopic remission % (n)	33% (8)	69% (18)*
Clinical remission % (n)	25% (6)	65% (17)†

*PENTASA vs placebo p=0.01
†PENTASA vs placebo p=0.005

95 patients in remission immediately after an acute episode of ulcerative proctitis and with an additional exacerbation within the previous 12 months were enrolled into a 12 month double-blind, placebo-controlled study to investigate the efficacy and safety of PENTASA Suppositories. They were randomised to receive either placebo or PENTASA Suppositories 1 g, 3 times a week. Remission was defined as no rectal bleeding, no mucous in the stools, no diarrhoea, no pain and no tenesmus, and an endoscopy score of 0 or 1. In the case of relapse the dose was increased to one suppository every day for 2-4 weeks or until remission. The primary endpoint was time to relapse. The mean time to relapse was 141.7 days in the PENTASA group and 84.9 days in the placebo group (p=0.09).

5.2 PHARMACOKINETIC PROPERTIES

The therapeutic activity of mesalazine appears to depend on local contact of the drug with the diseased area of the intestinal mucosa. PENTASA suppositories and enemas are designed to provide the distal part of the intestinal tract with high local concentrations of mesalazine and low systemic absorption. Scintigraphic studies have shown that suppositories cover the rectum whereas enemas reach the descending colon. An increase in enema volume extends the distribution along the colon.

Absorption

The absorption following rectal administration is relatively low and depends on the dose, pH, formulation and the extent of spread, the latter being dependent upon volume for the enemas. Based on urinary recovery of mesalazine and its N-acetyl metabolite in healthy volunteers under steady-state conditions an average of 10% of the dose was absorbed following administration of the 1 g suppository twice a day, whereas, about 15-20% is absorbed after administration of 1-2 g per day in enema form. In one study the 24 h 'Area Under the Curve' values of the metabolite were almost double those of the parent drug.

In patients with active ulcerative colitis, the urinary recovery was 13%.

Distribution

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). 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 as well as toxicologically inactive, but this still remains to be confirmed.

Excretion

After intravenous administration, the plasma half-life of mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 80 minutes. Due to an absorption-limited elimination following rectal administration, mesalazine has an apparent half-life of up to 7 hours, and the metabolite, acetyl-mesalazine, shows an apparent half-life of up to 11 hours.

Both substances are excreted in the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine and the faeces consist mainly of mesalazine.

Characteristics in patients

The systemic absorption following administration of PENTASA Enemas has been shown to be significantly decreased in patients with active ulcerative colitis compared to those in remission.

In patients with impaired liver and kidney function, 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

Genotoxicity

Mesalazine was negative in bacterial assays of gene mutation and in a mouse micronucleus test.

Carcinogenicity

There is no evidence of carcinogenicity in mice or rats treated with mesalazine in the diet at respective doses up to 2500 and 800 mg/kg/day for two years. These doses were associated with plasma concentrations of mesalazine and its metabolite N-acetyl-5-aminosalicylic acid of 32 fold or greater (mice) and 13 fold or greater (rats) than the peak plasma concentrations of these compounds at the maximal recommended human dose of the enema and the suppository.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Refer to SECTION 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES
Incompatabilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
Enemas: 3 years
Suppositories: 3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25ºC. Do not remove from packaging.

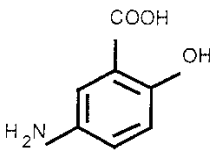
6.5 NATURE AND CONTENTS OF CONTAINER
PENTASA Enemas are supplied in packs of 7 plastic bottles. Each bottle is protected by an aluminium foil bag.

PENTASA Suppositories are supplied in packs of 5, 10, 28 and 30. Each suppository is protected in an aluminium foil blister. Not all pack sizes are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular Formula: $C_7H_7NO_3$ Molecular Weight: 153.14

Synonyms
5-aminosalicylic acid
5-amino 2-hydroxybenzoic acid
mesalamine

CAS Number
89-57-6

7 MEDICINE SCHEDULE (POISONS STANDARD)
(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

9 DATE OF FIRST APPROVAL

14 November 2003

10 DATE OF REVISION

31 August 2018

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

PENTASA® is a registered trademark of Ferring B.V.

Summary table of changes

Section Changed	Summary of new information
ALL	Updated PI format to comply with the new TGA form for providing product information format
2	Minor editorial change to add (1g/100mL) to the description of Pentasa Enema
3	Updated the description from Pentasa Rectal Suspension to Pentasa Enema to align with registered name
4.4	Addition of text under “Use in the elderly”
4.8	Addition of Photosensitivity as a rare adverse event, and alignment with MedDRA terminology