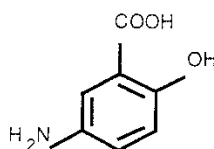


**PENTASA<sup>®</sup> Enemas and Suppositories****NAME OF THE MEDICINE**

Mesalazine (5-ASA)

**Synonyms:**

5-aminosalicylic acid

5-amino 2-hydroxybenzoic acid

C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>

CAS No. 89-57-6

MW: 153.14

**DESCRIPTION**

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

Pentasa Enemas contain 1g mesalazine 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.

**PHARMACOLOGY**

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

**Actions:**

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. Increased leukocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B<sub>4</sub> and increased free radical formation in the inflamed intestinal tissue, are all present in patients with inflammatory bowel disease. Mesalazine has *in vitro* pharmacological effects that inhibit leukocyte chemotaxis, decrease cytokine scavenger 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.

**PHARMACOKINETICS**

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.

**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.

**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 1g suppository twice a day, whereas, about 15 – 20% is absorbed after administration of 1-2g per day in enema form. In one study the 24h ‘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%.

**Elimination:**

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.

**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 proctosigmoiditis or proctitis, were randomised to receive a 100mL mesalazine enema of either 1g, 2g or 4g 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 1.

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

	Placebo	1g mesalazine	2g mesalazine	4g 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) <sup>†</sup>	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

<sup>†</sup>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 1g.

### **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 1g 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 2: Primary & Secondary Endpoints

	Placebo n=24	Pentasa n=26
Endoscopic remission % (n)	33% (8)	69% (18)*
Clinical remission % (n)	25% (6)	65% (17) <sup>†</sup>

\*Pentasa vs placebo p=0.01

<sup>†</sup>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 1g, 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).

### **INDICATIONS**

Enemas: Treatment of ulcerative proctosigmoiditis and/or treatment of left-sided ulcerative colitis

Suppositories: Treatment of ulcerative proctitis

### **CONTRAINDICATIONS**

Hypersensitivity to mesalazine or any other component of the product or salicylates.

Severe liver or renal impairment.

### **PRECAUTIONS**

Most patients who are intolerant or hypersensitive to sulfasalazine are able to take Pentasa without risk of similar reactions. However, caution is recommended when treating patients allergic to sulfasalazine because of risk of allergy to salicylates (also see 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.

Caution is recommended in patients with impaired liver function (also see Contraindications).

Mesalazine is not recommended for use in patients with renal impairment (see also Contraindications). Renal function should be monitored regularly in all patients (eg 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.

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 Adverse Effects).

Mesalazine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely with mesalazine. Treatment should be discontinued on suspicion or evidence of these adverse reactions (also see Adverse Effects).

## **USE IN CHILDREN**

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

## **CARCINOGENICITY/MUTAGENICITY**

There is no evidence of carcinogenicity in mice or rats treated with mesalazine in the diet at respective doses up to 2500 and 800mg/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. Mesalazine was negative in bacterial assays of gene mutation and in a mouse micronucleus test.

### **Impairment of Fertility:**

Oral administration of mesalazine at doses up to 400mg/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 400mg/kg/day in rats and rabbits, respectively.

Adequate human data on use of mesalazine during pregnancy are not available. Mesalazine is known to cross the placental barrier but the limited data available on the use of this compound in pregnant women do not allow assessment of possible adverse effects.

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 5-ASA during pregnancy were prospectively collected and pregnancy outcome was compared with that of a control group. The investigators concluded that 5-ASA does not represent a major teratogenic risk, as the reported rate of major malformations was within the expected baseline risk of the general population.

## **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.

## **DRUG 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 (eg 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.

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

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

## **ADVERSE EFFECTS**

The following table lists treatment related Adverse Reactions (of a frequency of  $\geq 1\%$ ) 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.

Adverse Reaction	Pentasa n = 217*	Placebo n=70
	n (%)	n (%)
<b>Gastrointestinal</b>		
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%)
<b>General</b>		
Pain Abdomen	7 (3.2%)	2 (2.9%)
Headache	3 (1.4%)	2 (2.9%)
Pain (Pain Back)	2 (0.9%)	1 (1.4%)
<b>Dermatological</b>		
Alopecia	3 (1.4%)	0
Rash (Mac Pap/Vesic Bull)	3 (1.4%)	0
<b>Other</b>		
Conjunctivitis	1 (0.5%)	1 (1.4%)
<b>Total Patients**:</b> n (%)	30 (13.8%)	7 (10.0%)

\*Includes all patients for three Pentasa dose groups, 1g/100mL, 2g/100mL & 4g/100mL.

\*\*Some patients experienced more than one event.

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

The following table represents the frequency of adverse effects based on clinical trials and reports from post-marketing surveillance for all formulations of Pentasa, including oral:

Common >1% and <10%	Nervous system disorders	Headache
	Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, vomiting
	Skin and subcutaneous tissue disorders	Rash (incl urticaria, erythematous rash)
Rare >0.01% and <0.1%	Cardiac disorders	Myo and pericarditis
	Gastro-intestinal disorders	Increased amylase, pancreatitis
Very rare <0.01%	Skin and subcutaneous tissue disorders	Reversible alopecia, bullous skin reactions including erythema multiforme and Stevens-Johnson syndrome
	Hepato-biliary disorders	Increased liver enzymes and bilirubin, hepatotoxicity (incl hepatitis, cirrhosis, hepatic failure)
	Renal and urinary disorders	Abnormal renal function (incl interstitial nephritis, nephrotic syndrome) urine discolouration
	Respiratory, thoracic and mediastinal disorders	Allergic lung reactions (incl. dyspnoea, coughing, allergic alveolitis, pulmonary eosinophilia, pulmonary infiltration, pneumonitis)
	Musculo-skeletal, connective tissue and bone disorders	Myalgia, arthralgia, Isolated reports of lupus erythematous-like reactions
	Blood and the lymphatic system disorders	Eosinophilia (as part of an allergic reaction), anaemia, aplastic anaemia, leukopenia (incl granulocytopenia), thrombocytopenia, agranulocytosis, pancytopenia
	Nervous system disorders	Peripheral neuropathy

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

## **DOSAGE AND ADMINISTRATION**

A visit to the toilet is recommended before administration of enemas and suppositories.

Enemas: The contents of one (1g) 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 (1g) suppository once daily.

## **OVERDOSAGE**

No rectal overdoses have been reported. There is no specific antidote. General supportive and symptomatic measures are recommended. Renal function should be closely monitored.

**PRESENTATION AND STORAGE CONDITIONS**

PENTASA Suppositories are supplied in packs of 28. Each suppository is protected in an aluminium foil blister.

PENTASA Enemas are supplied in packs of 7 plastic bottles. Each bottle is protected by an aluminium foil bag.

Store below 25°C. Do not remove from packaging.

**SPONSOR**

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

**POISON SCHEDULE**

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