

PENTASA[®] Tablets and Sachets

NAME OF THE MEDICINE

Mesalazine (5-ASA)

Synonyms:

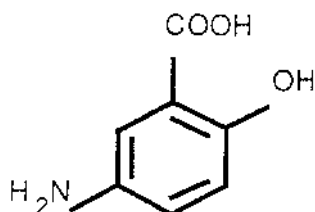
5-aminosalicylic acid

5-amino 2-hydroxybenzoic acid

C₇H₇NO₃

CAS No. 89-57-6

MW: 153.14



DESCRIPTION

PENTASA Tablets contain 500mg or 1g mesalazine as the active ingredient as well as the following inactive excipients: magnesium stearate, purified talc, povidone, ethylcellulose, microcrystalline cellulose.

PENTASA Sachets contain 1g or 2g mesalazine as the active ingredient as well as the following inactive excipients: ethylcellulose, povidone.

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 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 B₄ 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 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.

PHARMACOKINETICS

The therapeutic activity of mesalazine appears to depend on local contact of the drug with the diseased area of the intestinal mucosa.

PENTASA prolonged release granules and tablets consist of ethylcellulose-coated microgranules of mesalazine. Following administration and tablet disintegration, mesalazine is continuously released from the individual microgranules throughout the gastrointestinal tract in any enteral pH conditions.

The microgranules enter the duodenum within an hour of administration, independent of food co-administration. The average small intestinal transit time is approximately 3-4 hours in healthy volunteers.

Absorption:

Based on urinary recovery in healthy volunteers, 30-50% of the ingested dose is absorbed following oral administration, predominantly from the small intestine. Mesalazine is detectable in plasma 15 minutes after 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 0.3µg/mL, 1.2µg/mL and 1.9µg/mL after 1.5g, 4g and 6g daily dosages, respectively. For acetyl-mesalazine the corresponding concentrations are approximately 1.1µg/mL, 2.5µg/mL and 3.1µg/mL.

The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic absorption will be reduced.

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.

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 the 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 the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine and the faecal excretion consists mainly of mesalazine.

Characteristics in patients:

The delivery of mesalazine to the intestinal mucosa after oral administration is only slightly affected by pathophysiologic changes such as diarrhoea and increased bowel acidity 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. Likewise, a corresponding increase in faecal excretion has been seen.

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

Ulcerative colitis: Treatment of active disease

In a placebo-controlled, double-blind, randomised study of 374 patients aged 18 and over, with active mild to moderate ulcerative colitis, patients were treated with either placebo, or PENTASA 1g, 2g, or 4g daily for 8 weeks, given orally as 250mg slow release capsules. Three primary efficacy parameters were assessed at baseline and weeks 1, 4 and 8;

- Physician Global assessment; an investigator rating of the patient's improvement of symptoms since baseline, based on a scale of 1 to 6 (eg 1 = Complete relief of symptoms / 6 = Worsening in symptoms)
- Sigmoidoscopic Index (SI); an evaluation of the presence/severity of erythema, friability, granularity/ulceration, mucopus, and the appearance of mucosal vascular pattern, each assigned a value between 0 (normal) to 3 (severe) and totalled to provide an overall index score of between 0 - 15
- Treatment failure; which were those patients who were not receiving therapeutic benefit, defined as an increase of 5 points in SI and a worsening or no improvement in any symptoms (including trips to the toilet).

Primary Efficacy Results (intent-to-treat population)

n = 374	Placebo (n=90)	1g daily (n=92)	2g daily (n=97)	4g daily (n=95)
Physician Global Assessment <i>% of patients with complete or marked improvement of symptoms from baseline to last visit</i>	36%	45%	57%*	59%*
Sigmoidoscopic Index <i>Mean improvement in Index score from baseline to last visit (Mean±SE)</i>	-2.5 ± 0.45	-3.4 ± 0.45	-4.3* ±0.43	-5.0* ± 0.44
Treatment Failure	22%	17%	18%	9%*

*P < 0.05 vs placebo

Ulcerative Colitis: Maintenance of Remission

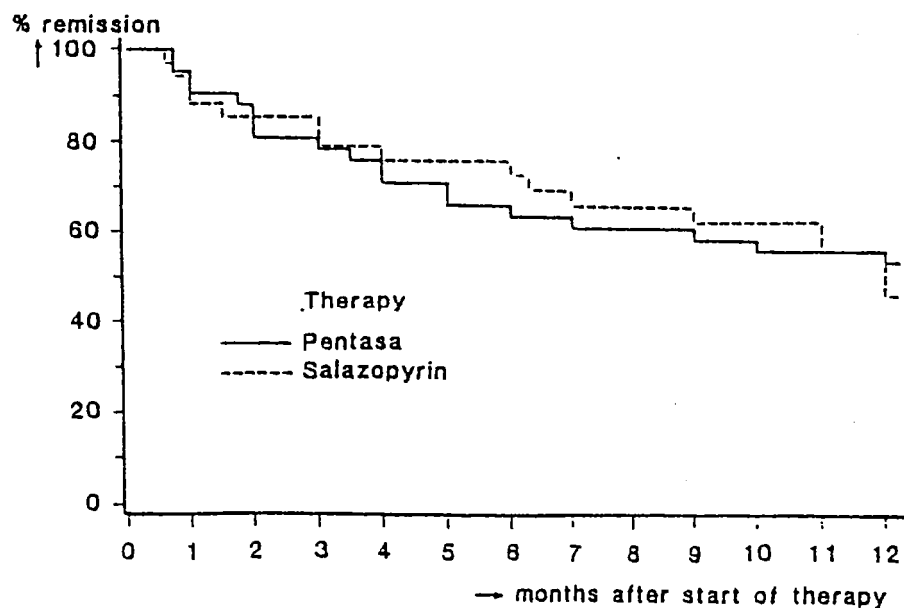
A double-blind study, double-dummy, randomised study comparing PENTASA 1.5g daily (administered as 250mg slow release tablets, three times a day) with sulfasalazine 3g daily (administered as 500mg enteric coated tablets, three times daily) treatment for 12 months, was conducted in 75 patients aged 18 years and over, with ulcerative colitis, who had been in remission for between 1 month and 5 years and had not taken steroids (either orally or as an enema) or azathioprine during at least 1 month before entry. Patients were assessed clinically, endoscopically and histologically before, and 3, 6, 9 and 12 months after the start of treatment. Endoscopy examined mucosal colour, vessel pattern, granularity, presence of valves, distention, polypoid structures, ulcers, spontaneous haemorrhage, and mucopurulent covering, and a wipe test was performed to determine friability. Endoscopy was scored as; normal, mild, moderate, severe abnormality or very severe abnormality. Histological assessment was made on the basis of biopsy examination for oedema and haemorrhage in the mucosa and submucosa, for quality and quantity of mucosal cellular infiltrate, and for epithelial architecture of the crypts and was scored as; normal, little inflammation, medium inflammation, severe inflammation, or UC in remission. Patients were assessed immediately if symptoms developed or if side effects occurred.

Patients were considered to have remained in remission if all data obtained at each visit were assessed as 'normal' or 'in remission'.

The data of 41 patients treated with PENTASA and 34 patients treated with sulfasalazine were included in life-table analysis for calculating remission rates (fig 1). No significant differences between the two treatments were revealed ($\chi^2 = 0.14$, df =1, p >0.70). The final remission rates were 54% for PENTASA and 46% for sulfasalazine, with 95% confidence intervals of 38%-69%

for PENTASA and 26%-64% for sulfasalazine. The difference is 8% in favour of PENTASA, with a 95% confidence interval of -16% to 31%.

Figure 1. Remission rates



In an investigator-blinded, randomised, controlled multi-centre study conducted in adult patients with mild to moderate ulcerative colitis in remission, 2g PENTASA once daily was non-inferior to 1g PENTASA twice daily with respect to relapse rate to 12 months.

Crohn’s Disease: Treatment of active disease

A meta-analysis was conducted of three double-blind, placebo-controlled, randomised, multi-centre studies in 615 patients aged 18 and over, of whom 304 were treated with up to 4g/day PENTASA administered as oral capsules and 311 were treated with placebo, for mild to moderate Crohn’s disease for a period of 16 weeks.

The primary efficacy variable used in these trials was the Crohn’s Disease Activity Index (CDAI), which included the following components; Sum of Liquid/very soft stools (per 7 days), Sum of abdominal pain rating (per 7 days), Sum of general well being ratings (per 7 days), use of loperamide or codeine, bodyweight, haematocrit, abdominal mass, Sum of symptoms.

Summary of intent-to-treat endpoint analysis of the CDAI Score for the 3 studies

Trial	Mean baseline CDAI ± SD & (range)		PENTASA 4g Change from baseline		Placebo Change from baseline		PENTASA 4g - placebo		
	PENTASA Group	Pl±±aceb o Group	n	Mean ± SE	n	Mean ± SE	Mean ± SE	95% confidence interval	P value
Crohn’s I	260±64 (86-381)	277±66 (112-460)	75	-72±13	80	-21±13	-52±18	(-88, -16)	0.005
Crohn’s II	248±76 (129-474)	255±79 (67-440)	75	-41±12	75	-35±12	-6±17	(-40, 27)	0.7
Crohn’s III	265±53 (136-431)	265±58 (118-428)	154	-72± 9	156	-64±9	-8±13	(-33, 16)	0.5
Overall effect (Meta-Analysis)				-63± 6		-45± 6	-18±9	(-35, -1)	0.04

The meta-analysis demonstrated that the use of PENTASA 4g/day for 16 weeks was associated with a statistically significant greater overall improvement in the CDAI from baseline to the final visit (P=0.04) when compared with placebo.

Crohn's Disease: maintenance of remission

In a randomised, double-blind, placebo-controlled study conducted in 293 patients aged 18 years and over, with Crohn's Disease in remission, a daily 3 g dose of PENTASA was administered as 250mg capsules for a period of up to 48 weeks (with assessments at baseline, and weeks 4, 12, 24, 36, 48). Relapse was defined as a Crohn's Activity Index of >150, with at least a 60 point increase over baseline.

246 patients completed a minimum of 4 weeks treatment. Of these, thirty of the 118 patients (25%) who received PENTASA had a relapse compared with 47 of 128 (36%) receiving placebo (P = 0.056).

INDICATIONS

Treatment of mild to moderate Ulcerative Colitis and Crohn's Disease and maintenance of remission.

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).

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.

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 7 fold (mice) and 3 fold (rats) the peak plasma concentrations of these compounds at the maximal recommended human dose of the granules and the tablets. 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.

As data are very limited, PENTASA should be used with caution during lactation and only if the potential risks 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 – 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 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

Ulcerative colitis

Treatment of active disease:

Adults: Individual dosage, up to 4g daily in divided doses

Maintenance treatment:

Adults: 2g once daily OR individual dosage, starting with 1.5-2g daily in divided doses

Crohn's disease*Treatment of active disease:*

Adults: Individual dosage, up to 4g daily in divided doses

Maintenance treatment:

Adults: Individual dosage, up to 4g daily in divided doses

The contents of the sachet should be emptied onto the tongue and washed down with some water or juice.

To facilitate swallowing, the tablets may be dispersed in 50mL of cold water. Stir and drink immediately. Do not crush or chew the tablets or granules.

OVERDOSAGE

Acute experience in animals: Single oral doses of mesalazine up to 5g/kg in pigs or a single intravenous dose of mesalazine at 920mg/kg in rats were not lethal.

Human experience: No overdoses have been reported.

Management of overdose in man: There is no specific antidote. General supportive and symptomatic measures are recommended. Renal function should be closely monitored.

PRESENTATION AND STORAGE CONDITIONS

PENTASA 500mg prolonged release tablets are white-grey to pale brown, speckled round tablets with breakmark and embossing: 500 mg on one side, PENTASA on the other side. They are supplied in blister packs of 30 and 100 tablets.

PENTASA 1g prolonged release tablets are white-grey to pale brown speckled oval tablets with 'PENTASA' embossed on both sides. They are supplied in blister packs of 20, 60 and 120 tablets.

PENTASA 1g Sachets contain mesalazine 1g prolonged release granules. They are supplied in packs of 30, 50, 100, 120 and 150 sachets.

PENTASA 2g Sachets contain mesalazine 2g prolonged release granules. They are supplied in packs of 10, 15 and 60 sachets.

PENTASA Sachets contain cylindrical shaped granules that are white-grey to pale white brown in colour.

Not all pack sizes are being distributed in Australia.

Store below 25°C. Keep in original container.

SPONSOR

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POISON SCHEDULE

Prescription Medicine

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