PENTASA

mesalazine

1 PENTASA

PENTASA 500mg Prolonged release tablet
PENTASA 1g Prolonged release tablet
PENTASA 10mg/mL Enema
PENTASA 1g Suppository
PENTASA 1g, 2g or 4g Granules, prolonged-release

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prolonged release tablet 500mg: Contains 500mg mesalazine

Prolonged release tablet 1g: Contains 1g mesalazine

Enema: Contains 10mg/mL mesalazine

Suppository 1g: Contains 1g mesalazine

Granules, prolonged-release: Contains 1g, 2g or 4g mesalazine

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet 500mg: white grey to pale brown speckled round tablet with a break-mark. Embossed 500mg on one side, PENTASA on the other side. The score line is not intended for breaking the tablet.

Prolonged release tablet 1g: white-grey to pale brown, speckled, oval tablet. Embossed on both sides with PENTASA.

Enema: a white to slightly yellow suspension in purified water with a pH value between 4.4 and 5.0. Added buffering agents result is a slightly acidic suspension. Sodium metabisulphite is added as an antioxidant.

Suppository: a white to light tan spotted oblong compressed suppository, average weight 1580mg, 1cm diameter and 2.8cm long.

Granules, prolonged-release: white-grey to pale white brown cylindrical shaped granules, containing 1g, 2g or 4g mesalazine.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prolonged release tablets 500mg and 1g, and granules 1g, 2g and 4g:
Treatment of mild to moderate ulcerative colitis or Crohn's disease.

Enemas:
Treatment of ulcerative proctosigmoiditis and left-sided colitis.

Suppositories:
Treatment of ulcerative proctitis.

4.2 Dose and method of administration

<u>Prolonged Release Tablets 500mg and 1g / Prolonged Release Granules 1g, 2g, 4g</u>

Ulcerative colitis
Treatment of active disease:
Adults: Individual dosage, up to 4g once daily or in divided doses.
Children: Individual dosage, starting with 20-30mg/kg bodyweight daily in divided doses.

Maintenance treatment:
Adults: Recommended dosage, 2g once daily.
Children: Individual dosage, starting with 20-30mg/kg bodyweight daily in divided doses.

Crohn's disease
Treatment of active disease:
Adults: Individual dosage, up to 4g daily in divided doses.
Children: Individual dosage, starting with 20-30mg/kg bodyweight daily in divided doses.

Maintenance treatment:

Adults: Individual dosage, up to 4g daily in divided doses.
Children: Individual dosage, starting with 20-30mg/kg bodyweight daily in divided doses.

Paediatric population
There is only limited documentation for effect in children.

Method of Administration:
PENTASA tablets or granules must not be chewed.

Tablets:
To facilitate swallowing, the tablets may be dispersed in 50ml of cold water. Stir and drink immediately.

Sachets:
The contents of the PENTASA granules sachet should be emptied onto the tongue and washed down with some water or orange juice.

Alternatively, the entire content of the sachet can be taken with yoghurt and consumed immediately.

Enema 10mg/mL
Adults: 1g mesalazine (100ml enema) at bedtime for 2-3 weeks.
Children: Reduced dose based on body weight. Generally, 10-20mg/kg body weight per day.Topical treatment can also be administered as maintenance treatment.

Shake the enema container well before use.

Suppository
1 suppository 1-2 times daily.

Paediatric population
There is little experience and only limited documentation for an effect in children.

NOTE: A visit to the toilet is recommended before administration of enemas and suppositories. See separate instructions for use.

4.3 Contraindications
Hypersensitivity to mesalazine, or any of the excipients (listed in section 6.1), or salicylates.

Severe liver and/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 risk of similar reactions. However, caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, and severe headache and/or the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other signs of hypersensitivity, therapy should be discontinued immediately.

Patients with inflammatory bowel disease are at risk of developing nephrolithiasis. Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content.
It is recommended to ensure adequate fluid intake during treatment.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches.

Hepatic Impairment

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

Renal Impairment
The medicine is not recommended for use in patients with renal impairment. The renal function should be regularly monitored (e.g. serum creatinine), especially during the initial phase of treatment. Urinary status (dip sticks) should be determined prior to and during treatment at the discretion of the treating physician. 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.

Pulmonary disease
Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment; please refer to section 4.8.

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

Blood dyscrasias
Serious blood dyscrasias have been reported very rarely with mesalazine. A blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. 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.

As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional symptoms occur, these tests should be performed immediately.

4.5 Interaction with other medicines and other forms of interaction

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.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

PENTASA should be used with caution during pregnancy and lactation and only if the potential benefits outweigh the possible hazards in the opinion of the physician.

Pregnancy (Category C)

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. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, parturition or postnatal development. Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in newborns of mothers being treated with PENTASA.

In one single case after long-term use of a high dose of mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

Breast-feeding

Mesalazine is excreted in breast milk. The mesalazine concentration in breast milk is lower than in maternal blood, whereas the metabolite - acetyl-mesalazine - appears in similar or increased concentrations. There is limited experience of the use of oral mesalazine in lactating women. No controlled studies with PENTASA during breast-feeding have been carried out. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. If the infant develops diarrhoea, breast-feeding should be discontinued.

Fertility

Animal data on mesalazine show no effect on male and female fertility.

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 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions seen in clinical trials are diarrhoea, nausea, abdominal pain, headache, vomiting and rash. Hypersensitivity reactions and drug fever may occasionally occur, including severe cutaneous adverse reactions, such as Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4)

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

Tabulated summary of adverse reactions

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance				
MedDRA Organ Class	**Common ≥1/100 to <1/10**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**Not known**
Blood and the lymphatic system disorders			Altered blood counts (Anemia, aplastic anemia, agranulocytosis, neutropenia), leukopenia (including granulocytopenia), pancytopenia,	

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance				
MedDRA Organ Class	**Common ≥1/100 to <1/10**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**Not known**
			thrombocytopenia, and Eosinophilia (as part of an allergic reaction).	
Immune system disorders			Hypersensitivity reaction, anaphylactic reaction	
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy	
Cardiac disorders		Myocarditis* 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 transaminases, 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, erythema multiforme,	Steven-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN), Drug reaction with Eosinophilia and Systemic Symptoms (DRESS).
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	Nephrolithiasis*** Urine discolouration

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance				
MedDRA Organ Class	**Common ≥1/100 to <1/10**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**Not known**
			syndrome, renal insufficiency)	
Reproductive system disorders			oligospermia (reversible)	
General disorders and administration site conditions	Anal discomfort, irritation at the application site, pruritis (anal), tenesmus (only with rectal form)		Drug fever	

(*) The mechanism of mesalazine-induced myocarditis 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.
(***) See section 4.4 for further information
It is important to note that several of these disorders can also be attributed to the inflammatory bowel disease itself.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

There is limited clinical experience with overdose of PENTASA which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive. There have been reports of patients taking daily doses of 8 grams for a month without any adverse events. But since PENTASA is an amino salicylate, symptoms of salicylate toxicity such as acid-base balance disorder, hyperventilation, pulmonary edema, vomiting, dehydration and hypoglycaemia may occur. Symptoms of salicylate over dosage are well described in the literature.

Management of overdose in humans

Symptomatic treatment at hospital. Close monitoring of renal function.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Active ingredient: mesalazine
Chemical formula: $C_7H_7NO_3$
Molecular weight: 153.13
Structural formula: 5-aminosalicylic acid

Mechanism of action and pharmacodynamics effects

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 local effect on the inflamed intestinal tissue, rather than to systemic effect.

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 IBD. Mesalazine has *in vitro* and *in vivo* pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leucotriene 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.

The risk of colorectal cancer (CRC) is increased in ulcerative colitis, especially in patients with extensive disease, with a disease course >8 years, with a first-degree family history of CRC, or with comorbid primary sclerosing cholangitis. The risk for colitis-associated CRC has been estimated to be 2% at 10 years, 8% at 20 years, and 18% at 30 years after onset of ulcerative colitis.

Observed effects of mesalazine in experimental models and patient biopsies support the role of mesalazine in prevention of colitis-associated CRC, with downregulation of both inflammation dependent and non-inflammation dependent signalling pathways involved in the development of colitis-associated CRC.

5.2 Pharmacokinetic properties

General characteristics of the active substance

Disposition and local availability

The therapeutic activity of mesalazine most likely depends on a local contact of the medicine 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.

PENTASA suppositories and enemas are designed to provide the distal part of the intestinal tract with high concentrations of mesalazine and a low systemic absorption. Suppositories cover the rectum, whereas enemas have been shown to reach and cover the descending colon.

Absorption

Based on urine 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 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 500mgx3 and 2gx3, respectively, implying a dose-dependent acetylation, which may be subject to saturation.

Mean steady-state plasma concentrations of mesalazine are approximately 2µmol/l, 8µmol/l and 12µmol/l after 1.5g, 4g and 6g daily dosages, respectively. For acetyl-mesalazine the corresponding concentrations are 6µmol/l, 13µmol/l and 16µmol/l.

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

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 2g (1g 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%.

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 inactive, but this still remains to be confirmed.

Elimination

After intravenous administration the plasma half-life of mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 70 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 with the urine and faeces. The urinary excretion consists mainly of acetyl-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.

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

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. See section 4.4.

5.3 Preclinical safety data

Toxic renal effects have been demonstrated in all species tested. Rat and monkey dosages and plasma concentrations at the No Observed Adverse Effect Levels (NOAELs) exceed those used in humans by a factor of 2-7.2.

No significant toxicity associated with the gastrointestinal tract, liver or haematopoietic system in animals has been observed.

In vitro test systems and *in vivo* studies showed no evidence of mutagenic or clastogenic effects. Studies of the tumourigenic potential carried out in mice and rats showed no evidence of any substance-related increase in the incidence of tumours.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

Mesalazine is deemed not to pose a risk to the environment at the doses prescribed for use in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Prolonged-release tablets 500mg; 1g: Active ingredient: Non-medicinal ingredients:	 mesalazine 500mg or 1g magnesium stearate, talc, ethylcellulose, povidone, microcrystalline cellulose
Prolonged-release granules 1g, 2g and 4g: Active ingredient: Non-medicinal ingredients:	 mesalazine 1g, 2g or 4g ethylcellulose, povidone
Suppositories: Active ingredient: Non-medicinal ingredients:	 mesalazine 1g magnesium stearate, talc, povidone, macrogol 6000
Enemas: Active ingredient:	 mesalazine 10mg/ml

Non-medicinal ingredients:	disodium edetate, sodium metabisulfite, sodium acetate, purified water, hydrochloric acid for pH adjustment

6.2 Incompatibilities

None known.

6.3 Shelf life

Tablets, 500mg & 1g: 36 months

Enema, 10mg/mL: 36 months

Suppositories, 1g: 36 months

Granules, 1g, 2g & 4g: 24 months

6.4 Special precautions for storage

Store below 25°C. Keep in original container, protected from light.

6.5 Nature and contents of container

PENTASA prolonged release tablets 500mg double aluminium foil blisters of 10 tablets - boxes of 100 tablets.

PENTASA prolonged release tablets 1g double aluminium foil blisters of 10 tablets - boxes of 60 tablets and 120 tablets.

PENTASA prolonged-release granules 1g – 100 or 120 individually packed sachets of aluminium foil.

PENTASA prolonged-release granules 2g – 10 or 60 individually packed sachets of aluminium foil.

PENTASA prolonged-release granules 4g – 30 individually packed sachets of aluminium foil.

PENTASA enemas 10mg/mL – polyethylene bottles with a tip with a valve for rectal application. The bottles are supplied in nitrogen-filled aluminium foil bags. 100mL, boxes of 7x100mL.

PENTASA enema starter kit – 1 x 100mL bottle.

PENTASA suppositories 1g - double aluminium foil blisters packs of 28s or 30s.

PENTASA suppositories 1g – starter pack 2 x 1g suppositories.

Not all strengths of these products are currently available in New Zealand.

6.6 Special precautions for disposal and other handling

The enema is protected by an aluminium foil bag and should be used immediately after opening of the bag. The enema may colour the linen and toilet

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

PENTASA 500mg Prolonged release tablet:	1 November 1990
PENTASA 1g Prolonged release tablet:	22 July 2010
PENTASA 10mg/mL Enema:	20 October 1988
PENTASA 1g Suppository:	30 April 1992
PENTASA 1g Granules, prolonged-release:	25 September 1997
PENTASA 2g Granules, prolonged-release:	21 December 2006
PENTASA 4g Granules, prolonged-release:	12 November 2015

10 DATE OF REVISION OF THE TEXT

24 March 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of text regarding reports of severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS) as per EMA PRAC recommendation. Addition of text regarding urine discoloration as per EMA PRAC recommendation.
4.8	The AE frequency for drug reaction with eosinophilia and systemic symptoms (DRESS) and urine discolouration is changed.