AUSTRALIAN PRODUCT INFORMATION – PENTASA® (MESALAZINE) PROLONGED RELEASE TABLETS AND GRANULES

1 NAME OF THE MEDICINE

Mesalazine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PENTASA prolonged release tablets contain either 0.5 g or 1 g mesalazine as the active ingredient, and the following inactive excipients: magnesium stearate, purified talc, povidone, ethylcellulose, microcrystalline cellulose.

PENTASA prolonged release granules in sachets contain either 1 g, 2 g or 4 g mesalazine as the active ingredient, and the following inactive excipients: ethylcellulose, povidone.

3 PHARMACEUTICAL FORM

PENTASA 0.5 g prolonged release tablets are presented as white grey to pale brown, speckled round tablets with break mark and embossing: 500 mg on one side, PENTASA on the other side.

PENTASA 1 g prolonged release tablets are presented as white-grey to pale brown, speckled, oval tablets. Embossing on both sides: PENTASA.

PENTASA 1 g, 2 g, and 4 g prolonged release granules are presented as cylindrical shaped granules that are white-grey to pale white brown in colour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of mild to moderate ulcerative colitis and Crohn's disease and maintenance of remission.

4.2 DOSE AND METHOD OF ADMINISTRATION

Ulcerative colitis

Treatment of active disease:

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

Maintenance treatment:

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

Crohn's disease

Treatment of active disease:

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

Maintenance treatment:

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

Method of administration

Do not crush or chew the tablets or granules.

Tablets:

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

Sachets:

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

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

4.3 CONTRAINDICATIONS

Hypersensitivity to mesalazine or any of the excipients 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**).
Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systematic symptoms (DRESS). Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.

Treatment should be discontinued immediately in cases of acute intolerance reactions such as nausea, exacerbation of diarrhoea, abdominal cramps, acute abdominal pain, fever, 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.

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

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, a 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 tioguanine. Treatment should be discontinued on suspicion or evidence of these adverse reactions (also see **SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

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

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.

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

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

Use of mesalazine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalazine's main metabolite, N-acetyl-5-aminosalicylic acid. An alternative selective assay for normetanephrine should be considered.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

- 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 furosemide (frusemide) – possible attenuation of the diuretic effects
- Rifampicin – possible attenuation of the tuberculostatic effects.

Combination therapy with PENTASA and azathioprine, or 6-mercaptopurine or tioguanine 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 the dosage regime of the thiopurines should be adjusted accordingly.
The concomitant use of mesalazine with other known nephrotoxic agents, such as non-steroidal anti-inflammatory drugs (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.

NSAIDS 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 NSAIDS 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.

As data are very limited, PENTASA should be used with caution during lactation and only if the potential benefits outweigh the possible hazards in the opinion of the physician. Hypersensitivity reactions, like diarrhoea, in the nursing infant cannot be excluded.

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)

Summary of the safety profile

Hypersensitivity reactions and drug fever may occasionally occur. Severe cutaneous adverse reactions (SCARs), 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Mesalazine may be associated with an exacerbation of the symptoms of colitis in those patients who have previously had such problems with sulfasalazine.

Table 1 below represents the frequency of adverse effects based on clinical trials and reports from post-marketing surveillance for all formulations of PENTASA, including orals:

Table 1.

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 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,	
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	
Hepatobiliary 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, and erythema multiforme, Drug Reaction with Eosinophilia nd Systemic Symptoms (DRESS)	Stevens-Johnson Syndrome (SJS) /Toxic epidermal necrolysis (TEN)
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***	Nephrolithiasis***
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 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

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

In the MOTUS study the incidences of nausea were 4.9% and 2.0% in the 4 g once daily and 2 g twice daily groups respectively. All events of nausea were mild to moderate in intensity and resolved; none led to withdrawal from the trial.

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 http://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. Since PENTASA is an aminosalicylate, 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 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.

Observed effects of mesalazine in experimental models show downregulation of both inflammation dependent and non-inflammation dependent signalling pathways involved in the development of colitis-associated colorectal cancer (CRC).

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 1 g, 2 g, or 4 g daily for 8 weeks, given orally as 250 mg slow release capsules. Three primary efficacy parameters were assessed at baseline and weeks 1, 4 and 8 (refer to Table 2 below)

- Physician global assessment; an investigator rating of the patient's improvement of symptoms since baseline, based on a scale of 1 to 6 (e.g. 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).

Table 2: Primary Efficacy Results (intent-to-treat population).

n=374	**Placebo (n=90)**	**1 g daily (n=92)**	**2 g daily (n=97)**	**4 g daily (n=95)**
Physician Global Assessment *% of patients with complete or marked Improvement of symptoms from baseline to last visit*	36%	45%	57%*	59%*
Sigmoidoscopic Index *Mean improvement in Index score from baseline to last visit (Mean±SE)*	-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

In an investigator-blinded, randomised, controlled multi-centre study (MOTUS trial) conducted in adult patients with active mild to moderate ulcerative colitis, 4 g PENTASA once daily was shown to be non-inferior to 2 g PENTASA twice daily in induction of remission after 8 weeks of treatment. In this trial a non-inferiority margin of 15% was calculated based on previously published studies. This margin is similar to those retained in comparable non-inferiority studies dealing with treatment of mild to moderately active UC (either assessing topical or systemic treatments) which vary from -15% to -20%.

The primary efficacy endpoint was the percentage of patients in clinical and endoscopic remission after 8 weeks of treatment, defined as an Ulcerative Colitis Disease Activity (UC-DAI) score ≤ 1. The statistical analysis was based on the intention-to-treat (ITT), modified ITT (mITT), and per protocol (PP) analyses with equal importance; remission rates are presented in Table 3 below.

Table 3: Remission Rate (UC-DAI score ≤1) at Week 8 (ITT, mITT, PP; LOCF).

	4 g once daily N (Weighted rate %)	**2 g twice daily N (Weighted rate %)**	**Difference (%) [95% CI]**	**P value**
ITT population	52/101 (52.1)	42/101 (41.8)	10.4 [-3.4; 24.1]	0.1402 (NS)
mITT population	52/89 (58.8)	42/90 (46.8)	12.0 [-2.6; 26.6]	0.1061 (NS)
PP population	48/79 (61.0)	37/77 (48.3)	12.8 [-2.7; 28.2]	0.1047 (NS)

CI 95%: 95% confidence interval; LOCF: Last observation carried forward

The results showed that PENTASA 4 g once daily was non-inferior to the reference regimen, PENTASA 2 g twice daily in patients with active UC treated for 8 weeks in all three study populations.

Ulcerative Colitis: Maintenance of Remission

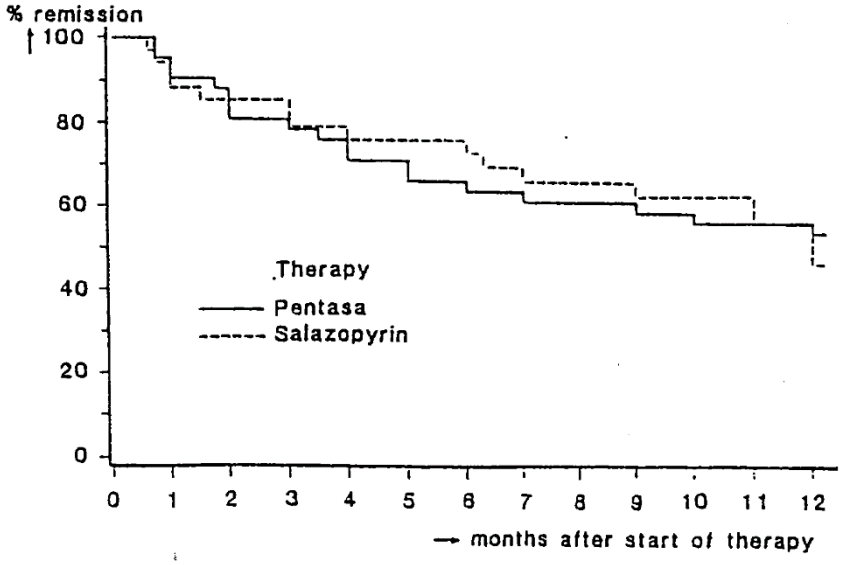
A double-blind , double-dummy, randomised study comparing PENTASA 1.5 g daily (administered as two 250 mg slow release tablets, three times a day) with sulfasalazine 3 g daily (administered as two 500 mg enteric coated tablets, three times a day) treatment for 12 months, was conducted in 75 patients 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 (χ^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 (PODIUM trial) conducted in adult patients with mild to moderate ulcerative colitis in remission, 2 g PENTASA once daily was non-inferior to 1 g PENTASA twice daily with respect to relapse rate to 12 months.

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 (see **SECTION 5.1 PHARMACODYNAMIC PROPERTIES**).

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 4 g/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 (refer to Table 4 below).

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.

Table 4: Summary of intent-to-treat endpoint analysis of the CDAI Score for the 3 studies.

	Mean baseline CDAI ± SD & (range)		**PENTASA 4 g Change from baseline**		**Placebo Change from baseline**		**PENTASA 4 g - placebo**		
Trial	**PENTASA Group**	**Placebo 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 4 g/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 250 mg 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).

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 prolonged release granules and tablets consist of ethylcellulose-coated microgranules of mesalazine. Following administration of the tablets and granules, and the disintegration of the tablets, 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 1-6 hours post-dose. Dosage regimens of 2 g twice daily and 4 g once daily of mesalazine result in comparable systemic exposures (AUC) over 24 hours and indicate the continuous release of mesalazine from the formulation over the treatment period. Steady-state is reached after a treatment period of 5 days following oral administration (refer to Table 5 below).

Table 5.

	Single dose		**Steady state**	
	C_{max} (ng/mL)	**AUC_{0-24} (h.ng/mL)**	**C_{max} (ng/mL)**	**AUC_{0-24} (h.ng/mL)**
Mesalazine				
2 g BID	5103.51	36,456	6803.70	57,519
4 g OD	8561.36	35,657	9742.51	50,742

Molecular weight of mesalazine: 153.13 g/mol; Acetyl-mesalazine: 195.17 g/mol

Mean steady-state plasma concentrations of mesalazine are approximately 0.3 µg/mL, 1.2 µg/mL and 1.9 µg/mL after 1.5 g, 4 g and 6 g daily dosages, respectively. For acetyl-mesalazine the corresponding concentrations are approximately 1.1 µg/mL, 2.5 µg/mL and 3.1 µg/mL.

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

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. The metabolic ratio of acetyl-mesalazine to mesalazine in plasma after oral administration ranges from 3.5 to 1.3 after daily doses of 500 mg x 3 and 2 g x 3, respectively, implying a dose dependent acetylation which may be subject to saturation.

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 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.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **SECTION 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Prolonged release tablets: 3 years
Prolonged release granules: 2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C. Keep in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Pentasa prolonged release tablets

PENTASA 0.5 g tablets are supplied in blister packs of 30 and 100 tablets.
PENTASA 1 g tablets are supplied in blister packs of 20, 60 and 120 tablets.

Pentasa prolonged release granules

PENTASA 1 g granules are supplied in packs of 30, 50, 100, 120 and 150 sachets.
PENTASA 2 g granules are supplied in packs of 10, 15 and 60 sachets.
PENTASA 4 g granules are supplied in packs of 8 and 30 sachets.

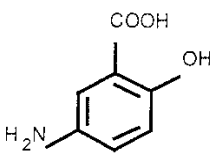
Not all pack sizes are being distributed in Australia.

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: 153.13

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
Toll free: 1800 337 746

9 DATE OF FIRST APPROVAL

Tablets 0.5 g: 2 January 2007
Tablets 1 g: 16 April 2010
Sachets 1 g and 2 g: 21 November 2006
Sachets 4 g: 14 August 2014

10 DATE OF REVISION

30 May 2023

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

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 discolouration as per EMA PRAC recommendation.
All	Editorial changes.