

## PENTASA

mesalazine

### **Presentation**

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, and containing 500mg mesalazine (5-aminosalicylic acid).

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

Enema: a white to slightly yellow suspension containing 10mg/mL mesalazine (5-aminosalicylic acid) in purified water. Added buffering agents result in 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. Contains 1g mesalazine.

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

### **Uses**

#### **Actions**

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

#### **Mechanism of action and pharmacodynamic 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 B<sub>4</sub>, 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 leukotriene production, and scavenge for free radicals 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**

##### **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.

#### *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.

#### *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 will be reduced.

The absorption following rectal administration is low, and depends on the dose, the formulation and the extent of spreading. 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%.

#### *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 with 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.

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.

#### **Indications**

##### Prolonged release tablets 500mg and 1g. and granules 1g and 2g:

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.

#### **Dosage and Administration**

##### **Prolonged Release Tablets 500mg and 1g/Prolonged Release Granules 1g and 2g**

##### Ulcerative colitis

###### *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:* 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.

PENTASA tablets or granules must not be chewed. To facilitate swallowing, the tablets may be dispersed in 50ml of cold water. Stir and drink immediately. The contents of the PENTASA granules sachet should be emptied onto the tongue and washed down with some water or orange juice.

**Enema**

Adults: 1g mesalazine (5-ASA) (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.

**Suppository**

1 suppository 1-2 times daily.

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

Shake the enema container well before use. The enema is protected by an aluminium foil bag and should be used immediately after opening of the bag.

**Contraindications**

Hypersensitivity to mesalazine, any other component of the product, or salicylates.  
Severe liver and/or renal impairment.

**Warnings and 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 sulphasalazine (risk of allergy to salicylates). In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

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. 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.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely. Serious blood dyscrasias have been reported very rarely with mesalazine. 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.

#### **Use in 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.

#### Use in Pregnancy (Category C)

Mesalazine is known to cross the placental barrier and its concentration in umbilical cord plasma is one tenth of the concentration in maternal plasma. The metabolite acetyl-mesalazine is found in the same concentration in umbilical cord and maternal plasma. From several observational studies no teratogenic effects are reported and there is no evidence of significant risk of use in humans. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in newborns of mothers being treated with PENTASA.

#### Use in Lactation

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.

#### **Effects On Ability To Drive And Use Machines**

Treatment with PENTASA is unlikely to affect the ability to drive and/or use machines.

#### **Adverse Effects**

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.

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

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance				
MedDRA Organ Class	Common (1-10%)	Rare (0.01-0.1%)	Very rare (<0.01%)	Not known
Blood and the lymphatic system disorders			eosinophilia (as part of an allergic reaction), altered blood counts anaemia, aplastic anaemia, leucopenia (incl. granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, pancytopenia	
Immune system disorders			pancolitis	hypersensitivity reaction
Nervous system disorders	headache	dizziness	peripheral neuropathy	
Cardiac disorders		myo*- and pericarditis		
Respiratory, thoracic and mediastinal disorders			allergic and fibrotic lung reactions (incl. dyspnoea, coughing, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	diarrhoea, abdominal pain, nausea, vomiting	increased amylase, acute pancreatitis*, flatulence		
Hepato-biliary disorders			increased liver enzymes, cholestasis parameters and bilirubin, hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)	
Skin and subcutaneous tissue disorders	rash (incl. urticaria, erythematous rash)		alopecia	
Musculoskeletal, connective tissue and bone disorders			myalgia, arthralgia, lupus erythematosus-like reactions	
Renal and urinary disorders			renal function impairment (incl. acute and chronic interstitial nephritis*,	

			nephrotic syndrome, renal insufficiency), urine discoloration	
Reproductive system disorders			oligospermia (reversible)	
General disorders and administration site conditions				drug fever

(\*) The mechanism of mesalazine-induced myo- and pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

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

### **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

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.

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

### **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**

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.

### **Management of overdose in man**

Symptomatic treatment at hospital. Close monitoring of renal function.

### **Pharmaceutical Precautions**

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

### **Medicine Classification**

Prescription Medicine.

### **Package Quantities**

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

PENTASA prolonged release tablets 1g: 60 tablets and 120 tablets.

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

PENTASA prolonged-release granules 2g – 10 or 60 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 1gm - boxes of 2, 4 or 8 double aluminium foil blisters, each containing 7 suppositories.

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

### **Instructions For Use/Handling**

The enemas are protected by an aluminium foil bag and should be used immediately after opening.

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

### **Further Information**

#### **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.

#### **Incompatibilities**

None known.

#### **List of excipients**

<b>Prolonged-release tablets 500mg; 1g:</b> Active ingredient: Non-medicinal ingredients:	mesalazine 500mg or 1g magnesium stearate, talc, ethylcellulose, povidone, microcrystalline cellulose
<b>Prolonged-release granules 1g and 2g:</b> Active ingredient: Non-medicinal ingredients:	mesalazine 1g or 2g ethylcellulose, povidone
<b>Suppositories:</b> Active ingredient: Non-medicinal ingredients:	mesalazine 1g magnesium stearate, talc, povidone, macrogol 6000
<b>Enemas:</b> Active ingredient: Non-medicinal ingredients:	mesalazine 10mg/ml disodium edetate dihydrate, sodium metabisulphite, sodium acetate trihydrate, purified water, concentrated hydrochloric acid ad pH 4.8

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

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