

Proposed packaging material	
Code	PENTAB500,1-I-MY,BN-06.01
Size	
Submission	☐ NDA ☐ Renewal ☒ Variation change detail no.: #270509
Code of previous version	PENTAB500,1-I-MY,BN-05.01
Changes	CCDS version 19: Strengthened warning related to nephrotoxicity following signal endorsement
	☒ CCDS version: - 19 ☐ Core PIL version: ☐ SPC country/version/date: ☐ LAC no.:
Name & Date	BRKH, 05-Oct-2025

PENTASA®

Prolonged Release Tablets 500 mg

Prolonged Release Tablets 1g

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mesalazine.

Each tablet contains 1g mesalazine.

Excipients: Magnesium stearate, talc, ethylcellulose, povidone, microcrystalline cellulose.

PHARMACEUTICAL FORM

Prolonged release tablet.

APPEARANCE

500mg: White grey to pale brown, speckled round tablets. Breakmark and embossing: 500 mg on one side, PENTASA on the other side.

1g: White-grey to pale brown, speckled, oval tablets. Embossing on both sides: PENTASA.

THERAPEUTIC INDICATIONS

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

POSODOLOGY AND METHOD OF ADMINISTRATION

Ulcerative colitis

Treatment of active disease:

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

Children 6 years of age and older: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:

Adults: Individual dosage. Recommended dosage, 1.5g to 2g mesalazine once daily. Can also be taken in divided doses.

Children 6 years of age and older: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

Crohn's disease

Treatment of active disease:

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

Children 6 years of age and older: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:

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

Children 6 years of age and older: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (recommended adult dose).

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Note for paediatric population:

There is only limited documentation for an effect in children (age 6-18 years).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

For oral use.

PENTASA® tablets must not be chewed. To facilitate swallowing, the tablets may be dispersed in 50 ml of cold water. Stir and drink immediately.

CONTRAINDICATIONS

Hypersensitivity to mesalazine, any of the excipients, or salicylates.

Severe liver or renal impairment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Most patients who are intolerant or hypersensitive to sulphasalazine 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, 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.

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 drug is not recommended for use in patients with renal impairment. The renal function should be monitored regularly (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. **Mesalazine treatment should be discontinued immediately if renal function deteriorates.** 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; see **Undesirable effects**.

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. As stated in section **Interaction with Other Medicinal Products and Other Forms of Interaction**, 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.

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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.

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.

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).

INTERACTION WITH OTHER MEDICINAL PRODUCTS 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.

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

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

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. The underlying condition itself (Inflammatory bowel disease/IBD) may increase risks for adverse pregnancy outcome.

Pregnancy

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. 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®.

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

Breastfeeding

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

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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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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, and 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 (see section **Special warnings and precautions for use**).

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 (cannot be estimated from the available data).
Blood and the lymphatic system disorders			Altered blood counts (anaemia, aplastic anaemia, agranulocytosis, neutropenia, leukopenia (including granulocytopenia), pancytopenia, thrombocytopenia and eosinophilia (as part of an allergic reaction))	
Immune system disorders			Hypersensitivity reaction including anaphylactic reaction	
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy	
Cardiac disorders		Myo*- and pericarditis*		

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MedDRA Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data).
Respiratory, thoracic and mediastinal 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,	Stevens-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 syndrome, renal insufficiency)	Nephrolithiasis*** Urine discolouration***
Reproductive system disorders			Oligospermia (reversible)	

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MedDRA Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data).
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.

(**) Photosensitivity: More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

(***) See section **Special warnings and precautions for use** for further information.

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

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® which does not indicate renal or hepatic toxicity. 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.

There have been reports of patients taking daily doses of 8 grams for a month without any adverse events.

There is no specific antidote and the management of overdose is supportive and symptomatic. The treatment at the hospital includes close monitoring of renal function.

PHARMACODYNAMIC PROPERTIES

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. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mesalazine.

Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B₄, and increased free radical formation in the inflamed intestinal

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tissue are all present in patients with IBD. The mechanism of action of mesalazine is 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- κ B) in the intestinal mucosa have been implicated. 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 slightly increased in ulcerative colitis.

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

However, data from metaanalyses, including both referral and non-referral populations, provide inconsistent clinical information regarding the benefit of mesalazine in the carcinogenesis risk associated with ulcerative colitis.

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 drug with the diseased area of the intestinal mucosa.

PENTASA® prolonged release tablets consist of ethylcellulose-coated microgranules of mesalazine. The tablet disintegrate upon administration to coated microgranules and enter the duodenum within an hour of administration, independent of food co-administration. Mesalazine is continuously released from the coated microgranules throughout the gastrointestinal tract in any enteral pH conditions.

Absorption:

Bioavailability of Pentasa® after oral administration can be estimated to approx. 30%, based on urine recovery data in healthy volunteers. Maximum plasma concentrations are seen 1-6 hours post-dose. A once-daily dosing regimen of mesalazine (1x4 g/d) and a twice-daily dosage (2x2 g/d) results in a comparable systemic exposure (AUC) over 24 hours and indicate a 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.

	Single dose		Steady State	
	Cmax (ng/mL)	AUC 0-24 (h'ng/mL)	Cmax (ng/mL)	AUC 0-24 (h'ng/mL)
Mesalazine				
2g BD	5103.51	36,456	6803.70	57,519
4g OD	8561.36	35,657	9742.51	50,742

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

The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic exposure may be increased.

Distribution:

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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) principally by NAT-1. 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 500mgx3 and 2gx3, respectively, implying a dose-dependent acetylation which may be subject to saturation.

Elimination:

Due to the continuous release of mesalazine from PENTASA® throughout the gastrointestinal tract, the elimination half-life cannot be determined after oral administration. However, once the formulation is not present in the GI tract elimination will follow the plasma half-life of orally or iv administered uncoated mesalazine, which is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes.

Characteristics in patients:

Pathophysiologic changes such as diarrhoea and increased bowel acidity observed during active inflammatory bowel disease has only a minor impact on the delivery of mesalazine to the intestinal mucosa after oral administration. A urine excretion 20-25% of the daily dose has been observed in subjects with accelerated intestinal transit. Likewise, a corresponding increase in faecal excretion has been seen.

INCOMPATIBILITIES

None known

SHELF LIFE

3 years

STORAGE

Store below 30°C in the original package, as the product is sensitive to light.

NATURE OF CONTAINER

Aluminum blisters. The top foil consists of an aluminum foil with heat-seal lacquer on the inner side and a lacquer on the outer side. The bottom foil consists of an aluminum foil with adhesive and PVC-film on the inner side and primer, adhesive and polyamide film on the outer side.

PACKING SIZES

Each blister foil contains 10 tablets.

500 mg: 100 tablets

1 g: 60 tablets

MANUFACTURER

Ferring International Center SA

Chemin de la Vergognausaz 50, 1162 St-Prex, Switzerland

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