NAME OF THE MEDICINAL PRODUCT
PENTASA® Sachet 2 g
Prolonged release granules 2 g

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains 2 g mesalazine.

Excipients: Ethylcellulose and Povidone.

PHARMACEUTICAL FORM
Prolonged release granules 2 g

Appearance of PENTASA® Sachet prolonged release granules 2 g: White-grey to pale white-brown granules.

THERAPEUTIC INDICATIONS
Treatment of mild to moderate ulcerative colitis.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology:
Ulcerative colitis
Treatment of active disease:
Adults: Individual dosage, up to 4 g given once daily or in divided doses.

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

Method of administration:
PENTASA® granules must not be chewed. The contents of the 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 yogurt and consumed 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 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.

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. 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. Please refer to section on 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.

Patients with inflammatory bowel disease are at risk of developing nephrolithiasis. Cases of nephrolithiasis with mesalazine content have been reported during treatment with mesalazine. Adequate fluid intake must be ensured 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.

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

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 (2-4 g, 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 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, 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 on 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*		
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			Increase in transaminases,	

disorders			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)	
General disorders and administration site conditions	Only with rectal form: Anal discomfort and irritation at the application site, pruritus (anal), rectal tenesmus		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 on 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 are limited clinical experience with overdose of PENTASA® which do not indicate renal or hepatic toxicity. 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 is 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.

Based on clinical results, the therapeutic value of mesalazine after oral 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 tissue are all present in patients with inflammatory bowel disease (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-κB) in the intestinal mucosa has 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 meta-analyses, 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 granules consist of ethylcellulose-coated microgranules of mesalazine 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 (1 × 4 g/d) and a twice-daily dosage (2 × 2 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				
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; 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:
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 500 mg × 3 and 2 g × 3, 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.

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.

INCOMPATIBILITIES
None known.

SHELF LIFE
2 years.

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original package, as the product is sensitive to light. Do not freeze.

NATURE AND CONTENTS OF CONTAINER

Individually packed sachets of aluminium foil.
PENTASA® Sachet 2g: Box of 60 sachets.

SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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

MANUFACTURER

Ferring International Center SA
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DATE OF REVISION

04 April 2023

PENSAC1,2-I-SG-08.01