NAME OF THE MEDICINAL PRODUCT
PENTASA® Suppositories 1 g

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each suppository contains 1 g mesalazine.
Excipients: Magnesium stearate, talc, povidone, macrogol 6000.

PHARMACEUTICAL FORM
Suppositories 1 g.

Appearance of PENTASA® suppositories 1 g: White to tan, spotted, oblong Suppositories.

THERAPEUTIC INDICATIONS
Treatment of ulcerative proctitis.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology:
1 suppository 1-2 times daily.

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

Method of administration:
1. A visit to the toilet is recommended before inserting a suppository.
2. Open the foil bag at the tear mark.
3. The suppository is inserted in the rectum until resistance is felt and disappeared again.
4. In order to facilitate the administration, the suppository can be moistured with water or moisture cream.
5. If the suppository is discharged within the first 10 minutes, another can be inserted.

CONTRAINDICATIONS
Hypersensitivity to mesalazine, any of the components of the product, or salicylates.
Severe liver and/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). 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 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.

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 Product 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.

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.

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
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 (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Blood and the lymphatic system disorders			Altered blood counts (Anaemia, aplastic anaemia, agranulocytosis, neutropenia, leucopenia (including granulocytopenia), pancytopenia, thrombocytopenia and eosinophilia (as part of an allergic reaction))
Immune system disorders			Hypersensitivity reaction including, anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),)
, 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 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).
Musculoskeletal, connective tissue and bone disorders			Myalgia, arthralgia, lupus erythematosus-like syndrome (systemic lupus erythematosus)

MedDRA Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Renal and urinary disorders			Renal function impairment (incl. acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency 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

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 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 and Crohn's disease.

Based on clinical results, the therapeutic value of mesalazine after 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 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-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.

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® suppositories 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.

Absorption:
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 2 g (1 g x 2), approximately 10% of the dose is absorbed after administration of suppositories.

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.

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.

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
3 years.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C. Store in the original package, as the product is sensitive to light.

NATURE AND CONTENTS OF CONTAINER
Double aluminium foil blisters.

Box of 4 blisters x 7 suppositories.

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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