PENTASA® Rectal Suspension 1 g

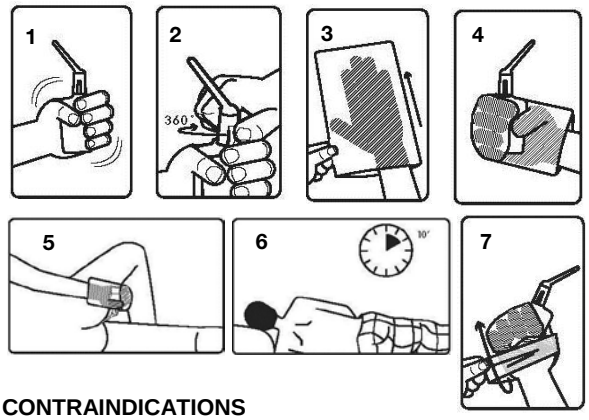
QUALITATIVE AND QUANTITATIVE COMPOSITION
Each bottle of rectal suspension contains 1 g mesalazine.
Excipients: disodium edetate, sodium metabisulphite, sodium acetate, purified water and hydrochloric acid for pH adjustment.

PHARMACEUTICAL FORM
Rectal suspension.

THERAPEUTIC INDICATIONS
Treatment of ulcerative proctosigmoiditis.

POSOLOGY AND METHOD OF ADMINISTRATION
Adults: 1 rectal suspension at bedtime.

INSTRUCTIONS FOR USE AND HANDLING
1. A visit to the toilet is recommended before administration of the rectal suspension.
2. Immediately before use take the rectal suspension bottle out of the aluminium foil pack and shake it well (Figure 1).
3. To break the seal twist the nozzle clockwise one full turn (the nozzle should then be in the same direction as before turning) (Figure 2).
4. Put your hand in one of the plastic disposal bags provided in the pack (Figure 3).
5. Hold the container as shown in the picture (Figure 4). Lubricate top part of rectal applicator.
6. To administer the rectal suspension, lie on your left side with the left leg straight and the right leg bent forward for balance. Carefully insert the applicator tip into the rectum. Maintain sufficient steady hand pressure while dispersing the bottle content. The bottle content should be applied within max. 30-40 seconds (Figure 5).
7. Once the bottle is empty, withdraw the tip with the bottle still compressed.
8. The rectal suspension should be retained in the bowel. Remain relaxed in the administration position for 5-10 minutes or until the urge to pass the rectal suspension has disappeared (Figure 6). Try to retain the rectal suspension overnight.
9. Roll the plastic disposal bag over the empty bottle (Figure 7). Discard it and wash your hands.



CONTRAINDICATIONS
Hypersensitivity to mesalazine, any of the excipients, or salicylates.
Severe liver or renal impairment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates).

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. 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 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.

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.

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 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. Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in newborns of mothers being treated with PENTASA®.

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. No controlled studies with PENTASA® during breast-feeding have been carried out. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded.

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)	Not known (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Eosinophilia (as part of an allergic reaction), anaemia, aplastic anaemia, leucopenia (incl. granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, pancytopenia	
Immune system disorders				Hypersensitivity reaction
Nervous system disorders	Headache		Peripheral neuropathy	
Cardiac disorders		Myo*- and pericarditis*		

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 mediastenal disorders			Allergic and fibrotic lung reactions (incl. dyspnoea, coughing, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, vomiting	Increased amylase, pancreatitis*		
Hepato-biliary disorders			Increased liver enzymes, bilirubin, hepatotoxicity (incl. hepatitis*, cirrhosis, hepatic failure)	
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)		Alopecia reversible	
Musculoskeletal, connective tissue and bone disorders			Myalgia, arthralgia, lupus erythematosus-like reactions	
Renal and urinary disorders			Renal function impairment (incl. interstitial nephritis*, nephrotic syndrome, renal insufficiency), Urine discolouration	
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.

OVERDOSE
Management of overdose in man: Symptomatic treatment at hospital. 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. 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. 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® rectal suspension are designed to provide the distal part of the intestinal tract with high concentrations of mesalazine and a low systemic absorption. Rectal suspension has 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: 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 2g (1g x 2), about 15-20% is absorbed after administration of rectal suspensions.

Distribution: Protein binding of mesalazine is approximately 50% and of acetyl-mesalazine about 80%.

Elimination: The plasma half-life of pure mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes. Both substances are excreted with the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine.

INCOMPATIBILITIES
None known.

SHELF LIFE
2 years.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30˚C in the original package, as the product is sensitive to light.

PACK SIZES
Polyethylene bottles with a tip for rectal application. The bottles are supplied in aluminium foil bags. Box of 7 bottles and 7 PE bags.

MANUFACTURER
Ferring-Léčiva, a.s.,
K Rybníku 475, 252 42 Jesenice u Prahy, Czech Republic

Date of revision: November 2016