570

1. NAME OF THE MEDICINAL PRODUCT

Salofalk® 250 mg/ 500 mg suppositories

Mesalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 250 mg/ 500 mg mesalazine as the medically active ingredient.

Excipient with known effect: cetyl alcohol (Salofalk 500 mg suppositories)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories

Appearance: white to cream-coloured, torpedo-shaped suppositories

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute episodes and maintenance of remission of ulcerative colitis that is limited to the rectum.

4.2 Posology and method of administration

Posology

Adults and elderly
For the treatment of acute episodes of ulcerative colitis
Two Salofalk 250 mg suppositories or one Salofalk 500 mg suppository are inserted into the rectum three times daily (equivalent to 1500 mg mesalazine daily), according to the individual clinical requirement.

For the maintenance of remission of ulcerative colitis
One Salofalk 250 mg suppository three times daily (equivalent to 750 mg mesalazine daily) inserted into the rectum.

Children and adolescents
There is little experience and only limited documentation for an effect in children.

Method of administration
When used three times daily, Salofalk 250 mg and 500 mg suppositories should be inserted into the rectum in the morning, at midday and at bedtime.

Treatment with Salofalk suppositories must be administered regularly and consistently, because only in this way can healing be successfully achieved.

An acute episode of ulcerative colitis generally subsides within 8 - 12 weeks. The duration of use is determined by the physician.

4.3 Contraindications

Salofalk suppositories are contraindicated in patients with
– known hypersensitivity to the active substance, salicylates or to any of the excipients listed in section 6.1
– severe impairment of hepatic or renal function

4.4 Special warnings and precautions for use

Blood tests (differential blood count, liver function parameters such as ALT or AST, serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. 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 3 months. If additional symptoms occur, these tests should be performed immediately.

Caution is recommended in patients with impaired hepatic function.

Salofalk suppositories should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered, if renal function deteriorates during treatment.

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.

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

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.
Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with a history of adverse drug reactions to preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with Salofalk suppositories. Should Salofalk suppositories cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Cetyl alcohol, an excipient of Salofalk 500 mg suppositories can cause local skin irritation (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.

In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine should be taken into account.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of Salofalk suppositories in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the fetus/ newborn child. To date no other relevant epidemiologic data are available. 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.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

Salofalk suppositories should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breast-feeding
N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk.
Only limited experience during lactation in women is available to date. Hypersensitivity reactions such as diarrhoea in the infant cannot be excluded. Therefore, Salofalk suppositories should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, the breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

The following undesirable effects have been observed after administration of mesalazine:

System organ class	*Frequency according to MedDRA convention*		
	Rare *(≥ 1/10,000; <1/1,000)*	Very rare *(< 1/ 10,000)*	Not known *(cannot be estimated from the available data)*
Blood and lymphatic system disorders		Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)	
Nervous system disorders	Headache, dizziness	Peripheral neuropathy	
Cardiac disorders	Myocarditis, pericarditis		

Respiratory, thoracic and mediastinal disorders		Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea, vomiting	Acute pancreatitis	
Renal and urinary disorders		Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*
Skin and subcutaneous tissue disorders	Photosensitivity	Alopecia	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia	
Immune system disorders		Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Hepatobiliary disorders		Changes in liver function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis	
Reproductive system disorders		Oligospermia (reversible)	

* See section 4.4 for further information.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

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

4.9 Overdose

There are rare data on overdosage (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal anti-inflammatory agents; aminosalicylic acid and similar agents
ATC code: A07EC02.

The mechanism of the anti-inflammatory action is unknown. The results of in-vitro studies indicate that inhibition of lipoxygenase may play a role.

Effects on the prostaglandin concentrations in the intestinal mucosa have also been demonstrated. Mesalazine (5-aminosalicylic acid/ 5-ASA) may also function as a radical scavenger of reactive oxygen compounds. On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

5.2 Pharmacokinetic properties

General considerations of mesalazine

Absorption
Mesalazine absorption is highest in the proximal gut regions and lowest in the distal gut areas.

Biotransformation
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and in the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43 % and 78 %, respectively.

Elimination
Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the faeces (major part), renally (varies between 20 % and 50 %, dependent on kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-Ac-5-ASA. About 1 % of total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

Salofalk suppositories specific

Distribution
Scintigraphic studies with technetium-labelled Salofalk 500 mg suppositories showed peak spread of the suppository that had melted due to body temperature after 2 - 3 hours. The spread was limited primarily to the rectum and rectosigmoid junction. Salofalk suppositories are thus particularly suitable for treating proctitis (ulcerative colitis of the rectum).

Absorption
After both a single administration and after several weeks of long-term treatment with 500 mg mesalazine three times daily as Salofalk suppositories, peak plasma concentrations of 5-ASA were in the range of 0.1 to 1.0 µg/ml, those of the main metabolite N-Ac-5-ASA were in the range of 0.3 to 1.6 µg/ml. Peak plasma concentrations of 5-ASA are partially reached within the first hour of application.

Elimination
After a single rectal dose of 500 mg mesalazine as Salofalk suppositories approx. 11 % (within 72 hours) was recovered in the urine, and after several weeks of long-term treatment with 500 mg mesalazine three times daily as Salofalk suppositories, approx. 13 % of the 5-ASA dose administered was recovered in the urine. Approximately 10 % of a single administered dose was eliminated via the bile.

5.3 Preclinical safety data

Preclinical data on mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction.

Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Salofalk 250 mg suppositories
Hard fat

Salofalk 500 mg suppositories
1. Hard fat
2. Docusate sodium
3. Cetyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original container in order to protect contents from light. Do not store above 25 °C.

6.5 Nature and contents of the container

Container (strip): PVC/polyethylene foil

Packs of 30 suppositories.

6.6 Special precautions for disposal and other handling

No special requirements.

Manufactured by Corden Pharma Fribourg AG, Zweigniederlassung Ettingen, Switzerland for Dr. Falk Pharma GmbH, Germany.

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