1. NAME OF THE MEDICINAL PRODUCT

Salofalk® 4 g/60 ml enemas
Salofalk® 2 g/30 ml enemas

Active substance: mesalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Salofalk 4 g/60 ml enema (= 60 g suspension) contains 4 g mesalazine as the active substance.
Each Salofalk 2 g/30 ml enema (= 30 g suspension) contains 2 g mesalazine as the active substance.

Excipients with known effect
Each Salofalk 4 g/60 ml enema contains 280.8 mg potassium metabisulphite and 60 mg sodium benzoate.
Each Salofalk 2 g/30 ml enema contains 140.4 mg potassium metabisulphite and 30 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal suspension

Appearance: cream-coloured to light, pale-brown homogeneous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute attacks of ulcerative colitis (a chronic inflammatory disease of the large bowel)

4.2 Posology and method of administration

Posology

Adults and elderly
The following dosage guidelines are generally applicable:
In patients with symptoms of acute inflammation, the content of 1 enema bottle (Salofalk 4 g/60 ml enemas) resp. 2 enema bottles (Salofalk 2 g/30 ml enemas) is administered into the intestine as an enema once daily at bedtime.

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

Method of administration

Rectal use.
The best results are achieved if the bowel is emptied before administration of the Salofalk enema.

The desired therapeutic result can only be achieved if Salofalk enemas are used regularly and consistently.

The duration of treatment is determined by the patient's doctor.

Acute attacks of ulcerative colitis usually regress after 8-12 weeks, after which Salofalk 2 g/30 ml / 4 g/60 ml enemas should not generally be used.

Preparation
- The bottle should be shaken for 30 seconds.
- Then the protective cap of the applicator removed.
- The bottle should be held at the top and bottom.

The correct position for administration is as follows:
- The patient should lie down on his/her left side with his/her left leg stretched out and right leg bent. This makes it easier for the enema to be administered and for the enema to be effective.

Administration of the rectal suspension
- The tip of the applicator should be inserted deep into the rectum.
- The bottle should be tipped downwards slightly and then squeezed slowly.
- Once the bottle is empty, the applicator tip should be slowly withdrawn from the rectum.
- The patient should remain lying down in this position for at least 30 minutes to allow the contents of the enema to spread throughout the rectum.
- If possible, the rectal suspension should be allowed to exert its effects all night.

4.3 Contraindications

Salofalk enemas must not be used in patients with
- known hypersensitivity to the active substance, to 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 like 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 enemas 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 enemas.

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 enemas. Should Salofalk enemas cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Salofalk 4 g/60 ml enemas and Salofalk 2 g/30 ml enemas contain potassium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

Each Salofalk 4 g/60 ml enema contains 60 mg sodium benzoate and each Salofalk 2 g/30 ml enema contains 30 mg sodium benzoate. Sodium benzoate may cause local irritation.

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 or 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 from the use of Salofalk enemas 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 epidemiological data are available. In one single case after long-term use of a high dose of mesalazine (2-4 g/day, 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 enemas 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 secreted in breast milk. Only limited experience with mesalazine during lactation in women is available to date. Hypersensitivity reactions such as diarrhoea in the infants cannot be excluded. Therefore, Salofalk enemas should only be used during breast-feeding if the potential benefit outweighs the potential 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 the 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

Mechanism of action
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 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.

Pharmacodynamic effects
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 proximal gut regions and lowest in distal gut areas.

Biotransformation
Mesalazine is metabolized 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 2 g/30 ml / 4 g/60 ml enemas specific

Distribution
An imaging study in patients with mild-to-moderate acute ulcerative colitis showed that the rectal suspension at the start of treatment and at remission after 12 weeks is distributed mainly in the rectum and sigmoid colon and to a lesser extent in the descending colon.

Absorption and elimination
No specific pharmacological studies on Salofalk 2 g/30 ml enemas are available.
In a study with Salofalk 4 g/60 ml enemas in ulcerative colitis patients in remission, peak plasma concentrations of 0.92 µg/ml 5-ASA and 1.62 µg/ml N-Ac-5-ASA were achieved after approximately 11-12 hours under steady-state conditions. The elimination rate was approximately 13% (45-hour value), with most (approximately 85%) being eliminated in the form of the metabolite, N-Ac-5-ASA.
The steady-state plasma concentrations of 5-ASA and N-Ac-5-ASA in children with chronic inflammatory bowel disease under treatment with Salofalk 2 g/30 ml enemas were 0.2-1.0 µg/ml and 0.4-2.0 µg/ml respectively whereas with Salofalk 4 g/60 ml enemas were 0.5-2.8 µg/ml and 0.9-4.1 µg/ml respectively.

5.3 Preclinical safety data

Preclinical data 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 tubule [pars convoluta] or of 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 2 g/30 ml enemas
Carbomer 35 000, potassium acetate, potassium metabisulphite (E224, max. 0.14 g, equivalent to max. 0.08 g SO_2), sodium benzoate (E 211), disodium edetate (Ph.Eur.), water, purified, xanthan gum

Salofalk 4 g/60 ml enemas
Carbomer 35 000, potassium acetate, potassium metabisulphite (E224, max. 0.28 g, equivalent to max. 0.16 g SO_2), sodium benzoate (E 211), disodium edetate (Ph.Eur.), water, purified, xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store at temperatures exceeding 30 °C. Store in the original sealed blister packs in order to protect from light.

6.5 Nature and contents of the container

Container
Salofalk 2 g/30 ml enemas:
Round, white, concertina-shaped LDPE bottle with a red protective LDPE cap.

Salofalk 4 g/60 ml enemas:
Round, white, concertina-shaped LDPE bottle with a green protective LDPE cap.

Not all presentations may be available locally.

Pack sizes
Packs containing 7 enemas.

6.6 Special precautions for disposal and other handling

No special requirements.

Batch released by Dr. Falk Pharma GmbH, Germany.

Date of revision of text: April 2023