PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCTS

Salofalk® Gastro-resistant Prolonged-release granules 500mg/sachet
Salofalk® Gastro-resistant Prolonged-release granules 1g/sachet
Salofalk® Gastro-resistant Prolonged-release granules 1.5g/sachet
Salofalk® Gastro-resistant Prolonged-release granules 3g/sachet
Mesalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of Salofalk granules 500mg contains 500 mg mesalazine.
Each sachet of Salofalk granules 1g contains 1000 mg mesalazine.
Each sachet of Salofalk granules 1.5g contains 1.5 g mesalazine.
Each sachet of Salofalk granules 3g contains 3 g mesalazine.

Excipients with known effect
Each sachet of Salofalk granules 500mg contains 1.0 mg aspartame and 0.02 mg sucrose.
Each sachet of Salofalk granules 1g contains 2.0 mg aspartame and 0.04 mg sucrose.
Each sachet of Salofalk granules 1.5g contains 3.0 mg aspartame and 0.06 mg sucrose.
Each sachet of Salofalk granules 3g contains 6.0 mg aspartame and 0.12 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant prolonged-release granules
Description: stick-formed or round, greyish white granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of acute episodes and the maintenance of remission of ulcerative colitis.

4.2 Posology and method of administration

Posology

Adults and the elderly
For the treatment of acute episodes of ulcerative colitis

Once daily, 1 sachet of Salofalk granules 3g, 1-2 sachets of Salofalk granules 1.5g, 3 sachets of Salofalk granules 1g or 3 sachets of Salofalk granules 500mg (equivalent to 1.5-3.0 g mesalazine daily) preferably to be taken in the morning according to the individual clinical requirement.
It is also possible to take the prescribed daily dose in three divided doses (1 sachet of Salofalk granules 500mg 3 times daily or 1 sachet of Salofalk granules 1g 3 times daily) if this is more convenient to the patient.

For the maintenance of remission of ulcerative colitis
The standard treatment is 0.5 g mesalazine 3 times daily (in the morning, at midday and in the evening) corresponding to a total dose of 1.5 g mesalazine per day.

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

Children 6 years of age and older
Active disease: To be determined individually, starting with 30-50 mg/kg bw/day once daily preferably in the morning or in divided doses. Maximum dose: 75 mg/kg bw/day. The total dose should not exceed the maximum adult dose.

Maintenance treatment: To be determined individually, starting with 15-30 mg/kg bw/day in divided doses. The total dose should not exceed the recommended adult dose.

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg and the normal adult dose to those above 40 kg.

Method of administration
The contents of the sachets of Salofalk granules should not be chewed. The granules should be taken on the tongue and swallowed, without chewing, with plenty of liquid.

Both in the treatment of acute inflammatory episodes and during long term treatment, Salofalk granules should be used on a regular basis and consistently in order to achieve the desired therapeutic effects.

The duration of use is determined by the physician.

4.3 Contraindications

Salofalk granules are contra-indicated in patients with
– 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 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 three months. If additional symptoms occur, these tests should be performed immediately.

Caution is recommended in patients with impaired hepatic function.

Salofalk granules 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 granules.

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 sulfasalazine should be kept under close medical surveillance on commencement of a course of treatment with Salofalk granules. Should Salofalk granules cause acute intolerance reactions, such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

This medicine contains 1 mg/2 mg/3 mg/6 mg aspartame in each sachet of Salofalk granules 500mg/1g/1.5g/3g. Aspartame is a source of phenylalanine. It may be harmful in patients with phenylketonuria (PKU).

Salofalk granules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take these medicines.

This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.
Lactulose or similar preparations which lower stool pH: possible reduction of mesalazine release from granules due to decreased pH caused by bacterial metabolism of lactulose.

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 granules 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 foetus/newborn child. To date no other relevant epidemiologic data are available. In one single case after long-term use of high dose 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, embryonal/foetal development, parturition or postnatal development.
Salofalk granules should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breastfeeding
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, like diarrhoea in the infant, cannot be excluded. Therefore, Salofalk granules should only be used during breastfeeding if the potential benefit outweighs the possible risk.
If the infant develops diarrhoea, the breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

Salofalk granules have no influence on the ability to drive and use machines.

4.8 Undesirable effects

See table at the end of this package leaflet.

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 antiinflammatory 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
Mesalazine, orally administered, acts predominantly locally at the gut mucosa and in the submucosal tissue from the luminal side of the intestine. It is important, therefore, that mesalazine is available at the regions of inflammation. Systemic bioavailability/plasma concentrations of mesalazine are therefore of no relevance for therapeutic efficacy, but rather a factor for safety. In order to realise this, Salofalk granules are gastric juice resistant and release mesalazine in a pH dependent manner, due to an Eudragit L coating, and prolonged manner, due to the matrix granule structure.

5.2 Pharmacokinetic properties

General considerations of mesalazine

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

Biotransformation
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and 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 %, depending on the 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 the total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

Salofalk granules specific

Distribution
Owing to the granule size of approx. 1 mm, transit from the stomach to the small intestine is fast.
A combined pharmacoscintigraphic/pharmacokinetic study showed that the compound reaches the ileocaecal region within approx. 3 hours and the ascending colon within approx. 4 hours. The total transit time in the colon amounts to about 20 hours.
Approximately 80 % of an administered oral dose is estimated to be available in the colon, sigmoid colon and rectum.

Absorption
Mesalazine release from Salofalk granules starts after a lag phase of about 2-3 hours. Peak plasma concentrations are reached at about 4-5 hours. The systemic bioavailability of mesalazine after oral administration is estimated to be approximately 15-25 %.
Food intake delays absorption by 1 to 2 hours but does not change the rate and extent of absorption.

Elimination
From a 3 x 500 mg daily mesalazine dose in long-term therapy, a total renal elimination of mesalazine and N-Ac-5-ASA under steady state conditions was calculated to be about 25 %. The unmetabolised excreted mesalazine part was less than 1 % of the oral dose. The elimination half-life in this study was 4.4 hours.

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 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.

5.4 Clinical trial information

The criteria used to evaluate the efficacy of the substance in the therapy of ulcerative colitis are frequency of bowel movements, rectal haemorrhage, abdominal pain, general well-being, temperature, extraintestinal manifestations, ESR, and haemoglobin. These criteria have been summarised in the clinical activity index (CAI) to evaluate the efficacy of treatment for ulcerative colitis.
The safety and efficacy of Salofalk granules (1.5 g to 3 g 5-ASA/day) was compared against mesalazine tablets (Salofalk 500 mg tablets, 1.5 g to 3.0 g 5-ASA/day) in a double-blind randomised multi-centre study in 233 patients with mild to moderately active ulcerative colitis over a period of 8 weeks. The primary efficacy criterion, complete response rate (per protocol analysis, PP) was very similar in the granules (68%) and the tablets (70%) groups. The efficacy analysis (PP) showed that more patients treated with mesalazine tablets (47%) had to increase the dose from 1.5 g mesalazine/day to 3.0 g mesalazine/day compared to patients treated with granules (38%). Similar results were obtained by the ITT (intention-to-treat) analysis: 39% of the granules group, 45% of the tablets group, i.e., more patients came into remission (49%) with the 1.5 g 5-ASA/day from granules than from tablets (43%). Granules, therefore, in total were at least as efficacious and as well tolerated as the tablets at the same dose. Subgroup analyses showed that the response rates to granules were higher in patients with high baseline disease activity (CAI>8) and with 1 or more extraintestinal manifestations than the tablets:

Parameters	Granules	Tablets
CAI ≤ 8	67%	74%
CAI > 8	65%	44%
Extraintestinal Manifestation:		
– none	69%	72%
– 1 or more	53%	36%

In another study, the efficacy and safety of Salofalk granules of different dosages (1.5 g, 3.0 g, 4.5 g/day) were compared in 321 patients with mild to moderately active ulcerative colitis in a double-blind manner for a treatment period of 8 weeks. Complete response (CAI ≤ 4) was obtained by 50% in the 1.5 g dose group, by 66% in the 3.0 g group (in comparison to 1.5 g: p = 0.014) and by 55% in the 4.5 g group (in comparison to 1.5 g: not significant, p=0.318). The 3.0 g/day dose appears to be the optimal dose.
In a double-blind, randomised comparative study, the efficacy and tolerability of once daily (o.d.) 3.0 g Salofalk granules was compared with three time daily (t.i.d.) 1.0 g Salofalk granules in 380 patients with active ulcerative colitis over a period of eight weeks. The data show that for Salofalk granules, a daily dose of 3 g mesalazine given o.d. is therapeutically equivalent to the conventional t.i.d. dosage regimen for the induction of remission (CAI ≤ 4) in patients with mild-to-moderate ulcerative colitis. The clinical remission rate in the PP analysis set (primary analysis) was 84.4% in the o.d. group and 81.3% in the t.i.d. group. The resulting p-value for the noninferiority test (pre-defined margin: -15%) was 0.0007 with a 95% CI of [-11.4%, 17.6%]. Remission rates in ITT analysis set were very similar, 80.8% in the o.d. group and 77.4% in the t.i.d. group. ITT test result (p = 0.0007) and 95% CI (-11.4%, 18.1%) agreed with the PP analysis. Once daily dosing of Salofalk granules was as safe and well tolerated as three times daily dosing of Salofalk granules.

Results of the various studies show that oral delayed release Salofalk granules are well tolerated in patients with ulcerative colitis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E 951); carmellose sodium (Ph.Eur.); citric acid; silica, colloidal anhydrous; hypromellose; magnesium stearate (Ph.Eur.); methacrylic acid-methyl methacrylate copolymer (1:1) (Ph.Eur.) (MW approx. 135000); methylcellulose; cellulose, microcrystalline; polyacrylate dispersion 40 % (Eudragit NE 40 D containing 2 % Nonoxynol 100); povidone K 25; simethicone; sorbic acid (Ph.Eur.); talc; titanium dioxide (E 171); triethyl citrate; vanilla custard flavouring (containing sucrose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Sachet of polyester/aluminium/polyethylene foil.
Each sachet of Salofalk granules 500mg contains 0.93 g granules.
Each sachet of Salofalk granules 1g contains 1.86 g granules.
Each sachet of Salofalk granules 1.5g contains 2.79 g granules.
Each sachet of Salofalk granules 3g contains 5.58 g granules.

Pack sizes
50 sachets, 100 sachets and 300 sachets Salofalk granules 500mg.
50 sachets, 100 sachets and 150 sachets Salofalk granules 1g.
35 sachets and 100 sachets Salofalk granules 1.5g.
20 sachets, 50 sachets and 100 sachets Salofalk granules 3g.

Not all presentations may be available locally.

6.6 Special precautions for disposal

No special requirements.

6.7 Name and address of product owner

Dr. FALK PHARMA GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

6.8 Date of Revision

August 2021

Undesirable Effects

System organ class	Frequency according to MedDRA convention				
	Common (≥ 1/100 to < 1/10)	*Uncommon (≥ 1/1,000 to < 1/100)*	Rare (≥ 1/10,000 to < 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, dyspepsia, 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			Arthralgia	Myalgia	
Immune system disorders				Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Hepatobiliary disorders			Cholestatic hepatitis	Hepatitis	
Reproductive system and breast disorders				Oligospermia (reversible)	
General disorders			Asthenia, fatigue		
Investigations		Changes in liver function parameters (increase in transaminases and parameters of cholestasis), changes in pancreatic enzymes (lipase and amylase increased), eosinophil count increased			

* 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.