SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salofalk 1.5g gastro-resistant prolonged-release granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of Salofalk 3g granules contains 3g mesalazine.

Excipients with known effect:
Each sachet of Salofalk 3g granules contains 6.0mg aspartame and 0.12mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release granules.
Description: stick-formed or round, beige or brownish granules, with or without yellowish surface parts.

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 elderly
For the treatment of acute episodes of ulcerative colitis:
Once daily 1 sachet of Salofalk 3g granules, 1 or 2 sachets of Salofalk 1.5g granules, 3 sachets of Salofalk 1000mg granules or 3 sachets of Salofalk 500mg granules (equivalent to 1.5 – 3.0g 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 500mg granules three times daily or 1 sachet of Salofalk 1000mg granules three 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 three times daily (in the morning, at midday and in the evening) corresponding to a total dose of 1.5g mesalazine per day. For patients known to be at increased risk for relapse for medical reasons or due to difficulties to adhere to application of three daily doses the dosing schedule can be adapted to 3.0g mesalazine given as a single daily dose preferably in the morning.

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 30-50mg/kg/day once daily preferably in the morning or in divided doses. Maximum dose: 75mg/kg/day. The total dose should not exceed the maximum adult dose.
Maintenance treatment: To be determined individually, starting with 15-30mg/kg/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 40kg; and the normal adult dose to those above 40kg.

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 cases of:
- hypersensitivity to the active substance, to salicylates or 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 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.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches).

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 drug reaction with eosinophilia and systemic symptoms (DRESS), 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 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 3mg aspartame in each sachet of Salofalk 1500mg granules. 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 a high dose of mesalazine (2-4g, 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/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 such as diarrhoea in the infant cannot be excluded. Therefore, Salofalk granules should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

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

4.8 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)	

Immune system disorders				Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
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)	
Gastro-intestinal disorders		Abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, vomiting, acute pancreatitis			
Hepatobiliary disorders			Cholestatic hepatitis	Hepatitis	
Skin and subcutaneous tissue disorders			Photosensi-tivity	Alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders			Arthralgia	Myalgia	
Renal and urinary disorders				Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*

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 drug reaction with eosinophilia and systemic symptoms (DRESS), 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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

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 submucous 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 therefore are 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 gut regions 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 %, 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 Granules specific:

Distribution:

Owing to the granule size of about 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 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 for 1 to 2 hours but does not change the rate and extent of absorption.

Elimination:
From a 3 x 500 mg daily mesalazine dose, a total renal elimination of mesalazine and N-Ac-5-ASA under steady state condition was calculated to be about 25 %. The un-metabolised 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E 951)
Carmellose sodium
Cellulose, microcrystalline
Citric acid
Hypromellose
Magnesium stearate
Methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L 100)
Methylcellulose
Polyacrylate dispersion 40% (Eudragit NE 40 D containing 2% Nonoxynol 100)
Povidone K 25
Silica, colloidal anhydrous
Simeticone
Sorbic acid
Talc

Triethyl citrate
Vanilla custard flavouring (containing sucrose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachet of polyester/aluminium/polyethylene-foil

Each sachet of Salofalk 1.5g granules contains 2.74g granules

Package sizes: 20, 30, 35, 45, 50, 60, 70, 90, 100 and 150 sachets Salofalk 1.5g granules

Not all package sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany
Tel: +49 (0)761 1514-0
E-Mail: zentrale@drfalkpharma.de

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