SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT

Salofalk® 500 Gastro-resistant tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Salofalk®500 gastro-resistant tablet contains 500 mg mesalazine.

Excipients with known effect: sodium carbonate and croscarmellose sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.

Appearance: Butter-yellow to ochre enteric-coated oblong formed tablets, lustreless with smooth surface; no cracking perceptible.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- For the treatment of acute episodes and the maintenance of remission of ulcerative colitis.
- For the treatment of acute episodes of Crohn's disease.

4.2 Posology and method of administration

Posology

Adults and elderly
Depending upon the clinical requirements in individual cases, the following daily doses are recommended.

	Crohn's disease	**Ulcerative colitis**	
	Acute episode	Acute episode	Prevention of recurrence/ long-term treatment
Mesalazine (active substance)	1.5 g - 4.5 g	1.5 g - 3.0 g	1.5 g
Salofalk®500 Gastro-resistant tablets	3 x 1 to 3 x 3	3 x 1 to 3 x 2	3 x 1

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 body weight /day in divided doses. Maximum dose: 75 mg/kg body weight /day. The total dose should not exceed the maximum adult dose.

Maintenance treatment (ulcerative colitis)
To be determined individually, starting with 15-30 mg/kg body weight /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.

Duration of treatment
The treatment of acute episodes of ulcerative colitis usually lasts 8 weeks. The duration of use is determined by the physician.

For maintenance of remission in ulcerative colitis, the dose can usually be reduced to 1.5 g mesalazine/day (adults and adolescents with a body weight over 40 kg) and 0.75 g mesalazine/day (children/adolescents).

Method of administration

Salofalk®500 Gastro-resistant tablets should be taken in the morning, at midday and in the evening, 1 hour before meals. They should be swallowed whole, not chewed, and taken with plenty of fluid.

Treatment with Salofalk®500 Gastro-resistant tablets should be administered regularly and consistently, both in the acute inflammatory stage and during maintenance therapy in order to achieve the desired therapeutic effect.

4.3 Contraindications

Salofalk® 500 Gastro-resistant tablets are contraindicated in patients with

- hypersensitivity to the active substance, 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.

Mesalazine should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered, if renal function deteriorates during treatment. If this is the case, Salofalk® 500 Gastro-resistant tablets should be discontinued immediately.

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).

Serious blood dyscrasias have been reported very rarely with mesalazine. Haematological investigations should be performed if patients suffer from unexplained haemorrhages, bruises, purpura, anaemia, fever or pharyngolaryngeal pain. Salofalk® 500 Gastro-resistant tablets should be discontinued in case of suspected or confirmed blood dyscrasia.

Cardiac hypersensitivity reactions (myocarditis, and pericarditis) induced by mesalazine have been rarely reported. Salofalk® 500 Gastro-resistant tablets should then be discontinued immediately.

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

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 mesalazine. Should Salofalk® 500 Gastro-resistant tablets cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

In rare cases, in patients who have undergone bowel resection/bowel surgery in the ileocoecal region with removal of the ileocoecal valve, it has been observed that Salofalk® 500 Gastro-resistant tablets were excreted undissolved in the stool, due to an excessively rapid intestinal passage.

This medicinal product contains 49 mg sodium per tablet, equivalent to 2.5% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 22% of the WHO recommended maximum daily intake for sodium. Salofalk® 500 Gastro-resistant tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

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 mesalazine 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 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/ foetal development, parturition or postnatal development.

Salofalk® 500 Gastro-resistant tabletsshould 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® 500 Gastro-resistant tablets 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

Mesalazine has no or negligible effects on the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been observed after administration of mesalazine

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	

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)**
				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)	
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, vomiting, acute pancreatitis			
Hepatobiliary disorders			Cholestatic hepatitis	Hepatitis	
Skin and subcutaneous tissue disorders	Rash, pruritus		Photosensitivity	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				Oligospermia (reversible)	

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)**
breast disorders					
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.

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 fulfil these criteria, Salofalk® 500 Gastro-resistant tablets are coated with Eudragit L; they are thus gastro-resistant and release of mesalazine is pH-dependent.

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® 500 Gastro-resistant tablets specific

Distribution
A combined pharmacoscintigraphic/pharmacokinetic study showed that Salofalk® 500 Gastro-resistant tablets reach the ileocoecal region after approximately 3-4 hours in fasting subjects and reach the ascending colon within approximately 4–5 hours. The total transit time in the colon is approximately 17 hours.

Absorption
Release of mesalazine from Salofalk® 500 Gastro-resistant tablets, begins after a lag-phase of approximately 3–4 hours. Peak plasma concentrations are reached after approximately 5 hours (ileocoecal region) and, at 3 x 500 mg mesalazine/ day under steady-state conditions, are 3.0 ± 1.6 µg/ml for mesalazine and 3.4 ± 1.6 µg/ml for the metabolite, N-Ac-5-ASA.

Elimination
The total renal elimination rate for mesalazine and N-Ac-5-ASA over 24 hours during multiple intake (3 x 1 Salofalk® 500 Gastro-resistant tablets, for 2 days; 1 tablet on the third day=examination day) was approximately 60%. The non-metabolised mesalazine fraction after oral administration was approximately 10%.

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 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

- Basic butylated methylacrylate copolymer (= Eudragit E)
- Calcium stearate
- Croscarmellose sodium
- Iron oxide (yellow) (E 172)
- Glycine
- Silica, colloidal anhydrous
- Hypromellose
- Macrogol 6000
- Methacrylic acid methyl methacrylate copolymer (1:1) (= Eudragit L)
- Cellulose, microcrystalline
- Sodium carbonate, anhydrous
- Povidone [K25]
- Talc
- Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use after the expiry date (EXP) on label

6.4 Special precautions for storage

Do not store at temperatures exceeding 30 °C.

Store in the original package. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Blister pack: PVC/PE/PVDC (orange-transparent) /aluminium blister foil

Package sizes:
Blister packs with 5 and 10 blisters corresponding to 50 and 100 gastro-resistant tablets. Each blister contains 10 gastro-resistant tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Manufactured by Losan Pharma GmbH, Neuenburg, Germany

Batch released by DR. FALK PHARMA GmbH, Freiburg im Breisgau, Germany

Imported by A. Menarini (Thailand) Limited , Bangkok

8 MARKETING AUTHORISATION NUMBER

To be determined by Thai FDA

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be determined by Thai FDA

10 DATE OF REVISION OF THE TEXT

July 2024