SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Salofalk® 500 (Suppositories)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One suppository contains 500 mg mesalazine as the medically active ingredient.

Excipient with known effect: cetyl alcohol

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories

Appearance: white to cream-coloured (colour shades that might be perceived as brownish or greyish may also occur), torpedo-shaped suppositories, even consistency and undamaged smooth surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults and elderly
One Salofalk® 500 (Suppositories) three times daily (equivalent to 1500 mg mesalazine daily) inserted into the rectum, according to the individual clinical requirement.

Paediatric population

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

Duration of treatment
The duration of use is determined by the physician.

Method of administration:
When used three times daily, Salofalk® 500 (Suppositories) should be inserted into the rectum in the morning, at midday and at bedtime.

Treatment with Salofalk® 500 (Suppositories) must be administered regularly and consistently, because only in this way can healing be successfully achieved.

4.3 Contraindications

Salofalk® 500 (Suppositories) are contraindicated in patients with:

- 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 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.

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 (Suppositories) 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. Hematological investigations should be performed if patients suffer from unexplained haemorrhages, bruises, purpura, anaemia, fever or pharyngolaryngeal pain. Salofalk® 500 (Suppositories) 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 (Suppositories) 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 (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 (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 mesalazine in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on the 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 (2-4 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/foetal development, parturition or postnatal development.

Salofalk® 500 (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® 500 (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

Mesalazine has no or negligible influence 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; <1/10)***	**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,	

System organ class	*Frequency according to MedDRA convention*			
	Common ***(≥ 1/100; <1/10)***	**Rare** ***(≥ 1/10,000; <1/1,000)***	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from the available data)**
			thrombocyto penia)	
Nervous system disorders		Headache, dizziness	Peripheral neuropathy	
Cardiac disorders		Myocarditis, pericarditis		
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospas m, 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	Rash, pruritus	Photosensiti vity	Alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), 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	

System organ class	*Frequency according to MedDRA convention*			
	Common ***(≥ 1/100; <1/10)***	**Rare** ***(≥ 1/10,000; <1/1,000)***	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from the available data)**
			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 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
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 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® 500 (Suppositories) specific

Distribution
Scintigraphic studies with technetium-labelled Salofalk® 500 (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® 500 (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® 500 (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® 500 (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® 500 (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 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

1. Hard fat
2. Docusate sodium
3. Cetyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use this medicine after the expiry date which is stated on the strip for the Salofalk® 500 (Suppositories) and on the carton.

6.4 Special precautions for storage

Store in the original container in order to protect contents from light.
Do not store at temperature exceeding 25 °C.
Keep medicines out of the reach of children.

6.5 Nature and contents of container

Container (strip):
PVC/LDPE foil

Pack sizes:
Packs of 1, 2, 3, 4, 5 and 10 suppositories per strip and contain 1, 2, 3, 4, 5, 6, 10, 15, 20, 25, 50, and 100 strip(s) per carton
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by Corden Pharma Fribourg AG, Zweigniederlassung Ettingen, Ettingen, Switzerland

Batch released by Dr. Falk Pharma GmbH, Freiburg im Breisgau, Germany

Imported by
A. Menarini (Thailand) Limited, Bangkok

8. MARKETING AUTHORISATION NUMBER

1C 82/49

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 3-Feb-2006

10. DATE OF REVISION OF THE TEXT

Jul 2024