Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salofalk 1g Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 1 g mesalazine.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suppositories

Appearance: light beige coloured, torpedo-shaped suppositories

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute mild to moderate ulcerative colitis that is limited to the rectum (ulcerative proctitis).

4.2 Posology and method of administration

Posology

Adults and older people
One Salofalk 1g Suppository once daily (equivalent to 1 g mesalazine daily) inserted into the rectum.

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

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

Method of administration

For rectal administration only.

Salofalk 1g Suppositories should be administered preferably at bedtime.

Treatment with Salofalk 1g Suppositories must be administered regularly and consistently, because only in this way can healing be successfully achieved.

4.3 Contraindications

Salofalk 1g Suppositoriesare contraindicated in patients with:
- known hypersensitivity to salicylates or to the excipient 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 1g 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 1g 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 1g 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.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Patients with a history of adverse drug reactionsto preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with mesalazine. ShouldSalofalk 1g Suppositoriescause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

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 of 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 fetus/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, 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 1g 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 1g Suppositories 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 influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies involving 248 participants, approximately 3% experienced adverse reactions while receiving Salofalk 1g Suppositories. The most commonly reported ADRs were headache, in approximately 0.8%, and gastrointestinal side effects (constipation in approximately 0.8%; nausea, vomiting and abdominal pain in 0.4% each).

The following side effects have been reported with the use of mesalazine:

Organ Class System	*Frequency According to MedDRA Convention*			
	Common (≥ 1/100 to < 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, thrombocytopenia)	
Nervous system disorders		Headache, dizziness	Peripheral neuropathy	Idiopathic intracranial hypertension (see section 4.4)
Cardiac disorders		Myocarditis, pericarditis		
Respiratory, thoracic and			Allergic and fibrotic lung	

mediastinal disorders			reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders		Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation	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	Photosensitivity	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 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.

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 national reporting system:

HPRA Pharmacovigilance
Website: www.hpra.ie

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: Aminosalicylic acid and similar agents
ATC code: A07EC02

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.
On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

Clinical efficacy and safety of Salofalk® 1 g suppositories was evaluated in a multicentre phase III study, which included 403 patients with endoscopically and histologically confirmed mild to moderately active ulcerative proctitis. The mean disease activity index (DAI) at base line was 6.2 ± 1.5 (range: 3 – 10). Patients were randomised to treatment with one Salofalk® 1 g suppository (1 g OD group) or 3 suppositories containing 0.5 g mesalazine (0.5 g TID group per day for 6 weeks. The primary efficacy variable was clinical remission defined as DAI < 4 at the final visit or withdrawal. At the final per protocol analysis, 87.9% of the patients in the 1 g OD group and 90.7% of the 0.5 g TID group were in clinical remission (Intention-to-treat analysis: 1 g OD group: 84.0%; 0.5 g TID group: 84.7%). The mean change in DAI from baseline was -4.7 in both treatment groups. No drug-related serious AEs occurred.

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 %, dependenton kind of application, pharmaceuticalpreparation and route of mesalazinerelease, 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 1g suppositories specific:

Distribution:

Scintigraphic studies with a similar medicinal product, technetium-labelled mesalazine 500mg 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. It is assumed that Salofalk 1g suppositories act very similar and thus are particularly suitable for treating proctitis (ulcerative colitis of the rectum).

Absorption:
In healthy subjects mean peak plasma concentrations of 5-ASA after a singlerectal dose of 1g mesalazine (Salofalk 1 g Suppository) were 192 ± 125 ng/ml (range 19 – 557 ng/ml), those of the main metabolite N-Ac-5-ASA were 402 ± 211 ng/ml (range 57 – 1070 ng/ml). Time to reach the peak plasma concentration of 5-ASA was 7.1 ± 4.9 h (range 0.3 – 24 h).

Elimination:
In healthy subjects, after a single rectal dose of 1g mesalazine (Salofalk 1g Suppository) approx. 14 % of the administered 5-ASA dose were recovered in the urine during 48 hours.

5.3 Preclinical safety data

With the exception of a local tolerance study in dogs, which demonstrated good rectal tolerance, no preclinical studies have been performed with Salofalk 1g Suppositories.

Preclinical data on mesalazine 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

Hard fat

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original container in order to protect contents from light.
Do not store above 30°C.

6.5 Nature and contents of container

Container (strip): PVC/polyethylene film

Package sizes: 10, 12, 15, 20, 30, 60, 90
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0573/004/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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