Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salofalk gastro-resistant prolonged release granules in bottles

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dosage unit of 500 mg mesalazine corresponds to 930 mg gastro-resistant prolonged release granules.
Each dosage unit of 1000 mg mesalazine corresponds to 1860 mg gastro-resistant prolonged release granules.
Each dosage unit of 1500 mg mesalazine corresponds to 2790 mg gastro-resistant prolonged release granules.

For excipients, see 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 adminstration

Adults and elderly
For the treatment of acute episodes of ulcerative colitis:
Depending on the clinical requirements in the individual case, granules equivalent to 500 mg mesalazine three times daily or granules equivalent to 1000 mg mesalazine three times daily (equivalent to 1.5 – 3.0 g mesalazine daily).

For the maintenance of remission of ulcerative colitis:
Granules equivalent to 500 mg mesalazine three times daily (equivalent to 1.5 g mesalazine daily).

Children below 6 years of age:
Salofalk granules should not be used in children under 6 years of age because there is very limited experience with this age group.

Children older than 6 years of age and adolescents:
In acute attacks, depending on disease severity, 30-50 mg mesalazine/kg/day should be given in 3 divided doses. For maintenance of remission, 15-30 mg mesalazine/kg/day may be given in 2 divided doses. 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.

All patients
The Salofalk® granules should not be chewed. The Salofalk® granules should be taken on the tongue and swallowed, without chewing, with plenty of liquid.

For dispensing and exact dosage of the Salofalk® granules, please see the instructions under 6.6.

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

In general, an acute episode of ulcerative colitis subsides after 8-12 weeks; the dosage can then, in most patients, be reduced to the maintenance dose.

4.3 Contraindications

Salofalk granules are contraindicated in cases of:

- pre-existing hypersensitivity to salicylic acid and its derivatives or to any of the other constituents
- severe impairment of hepatic and renal function
- pre-existing gastric or duodenal ulcer
- haemorrhagic diathesis

4.4 Special warnings and special 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, controls are recommended 14 days after commencement of treatment, then a further two to three times at intervals of 4 weeks.

If the findings are normal, control examinations should be carried out every 3 months. If additional symptoms occur, control examinations should be performed immediately.

Caution is recommended in patients with impaired hepatic function.
Salofalk is not recommended in patients with impaired renal function.
Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

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

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 intolerability reactions such as cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

In patients with phenylketonuria it should be kept in mind that Salofalk granules contain aspartame as a sweetening agent, equivalent to the following quantities of phenylalanine:

Gastro-resistant prolonged release granules equivalent to:	Aspartame equivalent to the following quantity of phenylalanine:
500 mg mesalazine	0.56 mg
1000 mg mesalazine	1.12 mg
1500 mg mesalazine	1.68 mg
3000 mg mesalazine	3.36 mg

Salofalk granules should not be used for the treatment of children below the age of 6 years.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.

Interactions may occur during treatment with Salofalk granules and concomitant

administration of the following medicinal products. Most of these possible interactions are based on theoretical reasons:

- Coumarin - type anticoagulants:	possible potentiation of the anticoagulant effects (increasing the risk of gastrointestinal haemorrhage)
- Glucocorticoids:	possible increase in undesirable gastric effects
- Sulphonylureas:	possible increase in the blood glucose-lowering effects
- Methotrexate:	possible increase in the toxic potential of methotrexate
- Probenecid/sulphinpyrazone:	possible attenuation of the uricosuric effects
- Spironolactone/frusemide:	possible attenuation of the diuretic effects
- Rifampicin:	possible attenuation of the tuberculostatic effects
- Lactulose or similar preparations, which lower stool pH:	possible reduction of mesalazine release from granules due to decreased pH caused by bacterial metabolism

In patients who are concomitantly treated with azathioprine or 6-mercaptopurine, possible enhanced myelosuppressive effects of azathioprine or 6-mercaptopurine should be taken into account.

4.6 Pregnancy and lactation

There are no adequate data from the use of Salofalk gastro-resistant prolonged release 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 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.

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in woman is available to date. Hypersensitivity reactions like diarrhoea can not be excluded. Therefore, Salofalk granules should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the suckling neonate develops diarrhoea, then breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Gastrointestinal undesirable effects (rare, ≥0.01% - <0.1%):
Abdominal pain, diarrhoea, flatulence, nausea, vomiting

CNS-related undesirable effects (rare, ≥0.01% - <0.1%):
Headache, dizziness

Renal undesirable effects (very rare, <0.01%):
Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency

Hypersensitivity reactions (very rare, <0.01%):
Allergic exanthema, drug fever, bronchospasm, peri- and myocarditis, acute pancreatitis, allergic alveolitis, lupus erythematosus syndrome, pancolitis

Musculoskeletal disorders (very rare, <0.01%):
Myalgia, arthralgia

Blood and the lymphatic system disorders (very rare, <0.01%):
Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)

Hepato-biliary disorders (very rare, <0.01%):
Changes in hepatic function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis

Skin and appendages disorders (very rare, <0.01%):
Alopecia

4.9 Overdose

No cases of intoxication have been reported to date and no specific antidotes are known.
If necessary, intravenous infusion of electrolytes (forced diuresis) should be considered in cases of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agent
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.

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 a Eudragit L coating, and prolonged manner due to the matrix granule structure.

5.2 Pharmacokinetic properties

<u>General considerations of mesalazine:</u>

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 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 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame
Carmellose sodium
Citric acid
Silica colloidal anhydrous
Hypromellose
Magnesium stearate
Methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L 100)
Methylcellulose
Microcrystalline cellulose
Polyacrylate dispersion 40 % (Eudragit NE 40 D containing 2 % Nonoxynol 100)
Povidone K 25
Simeticone
Sorbic acid
Talc
Titanium dioxide (E 171)
Triethyl citrate
Vanilla custard flavouring (containing propylene glycol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

Shelf life after first opening of the container: 6 months.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

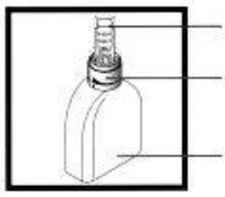
Container: Polypropylene bottles with integrated polystyrene measuring cup.

Package sizes: 50g, 100g, and 2 x 150g (300g)

Not all pack sizes will be marketed.

6.6 Instructions for use and handling

Salofalk gastro-resistant prolonged release granules in bottles contains a measuring cup with graduations allowing administration of 250mg, 500mg, 1000mg and 1500 mg doses of mesalazine.



A. Preparation of the bottle prior to first use

Remove measuring cup, remove and discard the tamper-evident seal

B. Dispensing the Salofalk granules

Open the bottle. After a quarter turn, the cap clearly locks into place and the dispenser is fully open (see arrow on the dose dispenser).

Hold the bottle in one hand and the measuring cup in the other. By tapping carefully with the finger, dispense the required dose of granules into the measuring cup (graduation marks for 250mg, 500mg, 1000mg and 1500 mg mesalazine). Pour the measured dose onto a desert-spoon and swallow.

Seal the bottle by rotating the cap and replacing the measuring cup..

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 573/3/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th August 2003

10 DATE OF REVISION OF THE TEXT

July 2005