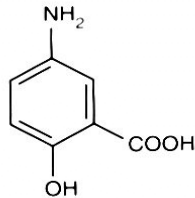


## PRODUCT INFORMATION

### SALOFALK® Suppositories

#### NAME OF DRUG



#### Mesalazine

Proper name: 5-Aminosalicylic Acid

Chemical name: 2-hydroxy-5-aminobenzoic acid, also referred to as 5-amino salicylic acid or 5-ASA

$C_7H_7NO_3 = 153.1$

CAS number- 89-57-6

#### DESCRIPTION

Mesalazine is a white to greyish, voluminous powder, slightly pink in colour. It is practically insoluble in ethanol (90%), methanol (70%), water, ether, and chloroform, soluble in HCl (warmed 10% solution); soluble in NaOH (10% solution, with salt formation).

SALOFALK suppositories contain mesalazine and hard fat.

#### PHARMACOLOGY

##### Pharmacodynamic properties

Mesalazine has been identified as the active component of sulfasalazine in inflammatory bowel disease and is thought to have a topical action. The mechanism of action by which mesalazine protects the mucosa in chronic inflammatory bowel disease is not yet fully known.

Mesalazine seems to act in multiple ways against several inflammatory mediators and principles. The results of *in vitro* investigations indicate that inhibition of lipoxygenase may play a role. Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated, as has an influence on leukotriene production. Mesalazine may also function as a radical scavenger of reactive oxygen compounds.

##### Pharmacokinetic Properties

##### General considerations:

The efficacy of mesalazine (5-ASA) appears to be determined not by the systemic but the local availability of the substance at the target site.

Metabolism of mesalazine occurs mainly in the intestinal mucosa and, to a lesser extent, in the liver. The main metabolite is N-acetyl-5-aminosalicylic acid, which is – like 5-ASA – predominantly eliminated by the renal and faecal routes. It appears to have no therapeutic activity or specific toxic effects. The acetylation step appears

irreversible. As metabolism occurs mainly in the intestinal mucosa, it has not been possible to differentiate between a rapid and slow acetylation form as in the case of sulfasalazine/sulfapyridine. The plasma protein binding of mesalazine and acetylated mesalazine is 43% and 78%, respectively.

Absorption of mesalazine decreases in the intestinal tract from proximal to distal. Because of low absorption rates from oral delayed release preparations or rectal applications forms, the main elimination route is via faeces. Absorbed mesalazine and N-acetyl-5-ASA are eliminated mainly via kidneys. Biliary excretion is a minor route of elimination.

There is little pharmacokinetic data available for rectal administered mesalazine in children. There is no pharmacokinetic data in the elderly using SALOFALK suppositories.

### **SALOFALK suppositories**

The mean peak plasma concentrations of mesalazine after a single rectal dose of 1 g mesalazine (SALOFALK 1 g suppository) were  $192 \pm 125$  ng/mL (range 19 – 557 ng/mL), those of the main metabolite N-Acetyl-5-ASA were  $402 \pm 211$  ng/mL (range 57 – 1070 ng/mL). Time to reach the peak plasma concentration of mesalazine was  $7.1 \pm 4.9$  hr (range 0.3 – 24 hr). The plasma levels following rectal administration are lower than those following oral administration.

Pharmacokinetic data are summarised in the following table for SALOFALK 1 g suppositories once daily in 48 healthy subjects:

| Pharmacokinetic Parameters | Salofalk 1 g suppositories |                           |
|----------------------------|----------------------------|---------------------------|
|                            | Mesalazine Mean* [SD]      | N-Acetyl-5-ASA Mean* [SD] |
| $C_{max}$ [ng/mL]          | 192.36 [125.33]            | 401.58 [210.81]           |
| $t_{max}$ [hr]             | 7.06 [4.86]                | 8.81 [5.64]               |
| $t_{1/2}$ [hr]             | 8.27 [9.86]                | 10.80 [13.19]             |
| $AUC_{(0-24)}$ [hr*ng/mL]  | 1933.71 [1765.42]          | 4893.33 [3767.03]         |
| $Ae_{0-24h}$ [mg]          | 1.20 [1.07]                | 94.00 [69.21]             |
| $Ae_{0-48h}$ [mg]          | 1.43 [1.27]                | 111.32 [83.82]            |

\* Arithmetic means

After a single rectal dose of 1 g mesalazine (SALOFALK 1 g suppository) approximately 14% (sum of mesalazine and its metabolite N-acetyl-5-ASA) of the administered mesalazine dose was recovered in the urine during 48 hours.

Scintigraphic studies of technetium-labelled mesalazine 500 mg suppositories showed peak spread of the suppository that had melted due to body temperature occurred after 2-3 hours. The spread was limited primarily to the rectum and rectosigmoid junction.

## CLINICAL TRIALS

The criteria used to evaluate the efficacy of the substance in the therapy of ulcerative colitis are frequency of bowel movements, rectal haemorrhage, abdominal pain, general well-being, temperature, extraintestinal manifestations, erythrocyte sedimentation rate (ESR), and haemoglobin. These criteria have been summarised in the clinical activity index (CAI) to evaluate the efficacy of treatment for ulcerative colitis.

In a multi-centre, randomised, investigator blinded study (SAS-6/UCA) involving 403 patients over 6 weeks, the efficacy and safety of SALOFALK 1 g suppository once daily at bedtime in the therapy of acute ulcerative proctitis was demonstrated to be therapeutically equivalent to that of SALOFALK 500 mg suppository three times daily.

The primary efficacy variable was clinical remission, defined as Disease Activity Index (DAI) < 4 at the final visit. DAI is defined as the sum of the scores of four parameters: weekly stool frequency, weekly rectal bleeding, mucosal appearance and physician's rating of disease activity.

### Clinical remission results

|          |     | Number (%) of patients with clinical remission at the final/withdrawal examination |                                | Difference between proportions <sup>a</sup> [95% CI] | Shifted asymptotic $\chi^2$ test for comparing two rates <sup>b</sup> |
|----------|-----|--|--------------------------------|--|---|
|          |     | Salofalk 1 g Suppository OD  | Salofalk 0.5 g Suppository TID |  |   |
| Analysis | PP  | 160/182 (87.9%)  | 156/172 (90.7%)                | -2.8% [-9.2%, 3.6%]                                  | 3.463 <sup>c</sup>  |
|          | ITT | 168/200 (84.0%)  | 172/203 (84.7%)                | -0.7% [-7.8%, 6.4%]                                  | 3.790 <sup>c</sup>  |

OD, once daily; TID, three times daily

<sup>a</sup> Difference between proportions [Salofalk 1 g suppository OD – Salofalk 500 mg suppository TID]; asymptotic confidence interval (CI).

<sup>b</sup> 'Effect' = difference between proportions [Salofalk 1 g suppository OD – Salofalk 500 mg suppository TID] + 0.15).

<sup>c</sup> Inverse normal.

### Overview of number (%) of patients in PP population with a change in DAI, CAI, and EI from baseline to last observation carried forward (LOCF)

| Change      | DAI 1 <sup>a</sup>       |                            | CAI                      |                            | EI <sup>b</sup>          |                            |
|-------------|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|----------------------------|
|             | Salofalk 1 g Suppository | Salofalk 0.5 g Suppository | Salofalk 1 g Suppository | Salofalk 0.5 g Suppository | Salofalk 1 g Suppository | Salofalk 0.5 g Suppository |
|             | OD<br>n = 182            | TID<br>n = 172             | OD<br>n = 182            | TID<br>n = 172             | OD<br>n = 176            | TID<br>n = 164             |
| Remission   | 160 (87.9%)              | 156 (90.7%)                | 160 (87.9%)              | 159 (92.4%)                | 149 (84.7%)              | 147 (89.6%)                |
| Improvement | 17 (9.3%)                | 12 (7.0%)                  | 172 (94.5%)              | 161 (93.6%)                | 19 (10.8%)               | 10 (6.1%)                  |

OD, once daily; TID, three times daily;

DAI, disease activity index; CAI, clinical activity index; EI, endoscopic index

<sup>a</sup> Patients with (DAI) > 3 at baseline.

<sup>b</sup> Patients with EI ≥ 4 at baseline.

DAI=Remission: (DAI) < 4 at LOCF

CAI=Remission: CAI ≤ 4 at LOCF (= clinical remission).

EI=Remission: EI < 4 at final examination.

Results of the studies show that SALOFALK suppositories are well tolerated in patients with ulcerative proctitis.

## INDICATIONS

SALOFALK suppositories are indicated in the treatment of ulcerative proctitis.

## CONTRAINDICATIONS

SALOFALK suppositories are contraindicated in patients with the following:

- hypersensitivity to salicylic acid, salicylic acid derivatives, e.g. mesalazine/5-ASA
- hypersensitivity to any other ingredients in SALOFALK suppository
- severe impairment of hepatic and renal function

## PRECAUTIONS

SALOFALK should be given/used under medical supervision. SALOFALK is not recommended in patients with impaired renal function. The blood and renal status should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, checks are recommended 14 days after commencement of treatment, then a further 2 to 3 times at 4-weekly intervals. If the findings are normal, follow-up tests should be conducted every three months or immediately if additional signs of the disorder occur. To check renal function, it is recommended that levels of serum urea (BUN) and creatinine be determined as well as urine sediment examined. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

As mesalazine might cause blood dyscrasias, although rarely reported, and hepatic impairment due to hypersensitivity reactions, blood parameters, like blood counts and liver function and cholestasis parameters (e.g. ALT, AST, alkaline phosphatase,  $\gamma$ GT) may be monitored like the renal parameters. Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or sulfasalazine therapy, should be investigated in order to exclude pericarditis, hepatitis and pancreatitis either as adverse drug reactions to 5-ASA or secondary manifestations of inflammatory bowel disease.

SALOFALK should be used/given with caution in patients with pulmonary function impairment, particularly asthma and in patients with known hypersensitivity to sulfasalazine containing preparations. Treatment in the latter patients should be instituted with careful medical supervision. Treatment should be discontinued immediately if symptoms of acute intolerance, e.g. cramps, acute abdominal pain, fever, severe headache and skin rash, occur.

SALOFALK suppositories are generally not expected to affect the ability of patients to drive or operate machinery.

## Effects on fertility

Fertility and reproductive performance were not impaired in rats treated orally with mesalazine prior to and during mating (both sexes) and throughout gestation and lactation (females) at doses up to 320 mg/kg/day. This dose is less than the maximal

recommended clinical dose of SALOFALK tablets, and about the same as the maximal recommended clinical dose of SALOFALK granules, on a body surface area basis.

### **Use in pregnancy (Category C)**

There was no evidence of embryotoxicity or teratogenicity in rats and rabbits treated orally with mesalazine during the period of organogenesis at respective doses of up to 320 and 495 mg/kg/day. On a body surface area basis, these doses are about 0.5-2.5 times the maximal recommended clinical dose of SALOFALK tablets, and about 1.0-3.5 times the maximal recommended clinical dose of SALOFALK granules. Oral mesalazine does not indicate direct or indirect harmful effects with respect to parturition or postnatal development in animals.

Human data on use during pregnancy are limited. No adverse effect of mesalazine on pregnancy or on the health of the foetus/newborn child was shown. To date no other relevant epidemiologic data are available. In one single case after oral use of 2-4 g mesalazine per day during the 3<sup>rd</sup> and 5<sup>th</sup> months of pregnancy, renal failure in the neonate was reported. SALOFALK suppositories should only be used during pregnancy if the potential benefit outweighs the possible risk.

### **Use in lactation**

In rats, there were no adverse effects on dams or offspring from oral administration of mesalazine during late gestation and throughout lactation at doses up to 320 mg/kg/day. This dose is less than the maximal recommended clinical dose of SALOFALK tablets, and about the same as the maximal recommended clinical dose of SALOFALK granules, on a body surface area basis.

There has been a report of a patient receiving mesalazine suppositories during the lactation period. Twelve hours after the initial dose, the infant developed watery diarrhoea that disappeared on discontinuation of the mesalazine therapy but reappeared on rechallenge. There have been reports of mesalazine and of its metabolite N-acetyl-5-ASA found in breast milk. But, there is no experience with SALOFALK suppositories in lactating women. SALOFALK should not be used during lactation unless the likely benefit of treatment outweighs the potential hazard.

### **Paediatric use**

SALOFALK 1 g suppositories should not be used in children 12 years old and under, as there is little experience with this age group.

### **Use in the elderly**

Specific clinical data in only elderly patients for mesalazine are not available, but have been used in patients up to 75 years of age in clinical trials.

### **Carcinogenicity**

There was no evidence of carcinogenicity in rats treated with mesalazine in the diet for 127 weeks at doses up to 320 mg/kg/day, associated with plasma concentrations of mesalazine and N-acetyl-5-ASA of at least 15 fold the respective clinical plasma C<sub>max</sub> concentrations associated with a 1 g dose of SALOFALK suppository.

## Genotoxicity

There was no evidence of genotoxic potential with mesalazine in bacterial gene mutation assays, of chromosomal damage in mouse haematopoietic cells following a single oral dose, or of increases in sister chromatid exchange frequencies in Chinese hamster bone marrow following a single intraperitoneal dose.

## Interactions with other drugs

Studies to evaluate the potential interaction between SALOFALK and other drugs have not been performed. In common with other salicylates, interactions may occur during concomitant administration of mesalazine and the following drugs:

- Coumarin-type anticoagulants: possible potentiation of the anticoagulant effect action (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 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

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.

## Effects on laboratory tests

Not known to interfere with laboratory tests or physical diagnostic agents.

## ADVERSE EFFECTS

In a multi-centre, randomised, investigator blinded study (SAS-6/UCA) involving 403 patients with active ulcerative proctitis, the rate of patients reporting at least 1 adverse event is 2.5% and 3.4% in the 1 g and 500 mg suppository groups respectively. The adverse events reported are shown in Table I below.

**Table I**

| <b>Adverse Event</b>            | <b>Salofalk 1 g<br/>suppositories<br/>(n=200)</b> | <b>Salofalk 500 mg<br/>suppositories<br/>(n=203)</b> |
|---------------------------------|---|--|
| <i>Constipation</i>             | 2 (1.0%)  | 1 (0.5%)   |
| <i>Lipase increased</i>         | 1 (0.5%)  | 1 (0.5%)   |
| <i>Platelet count decreased</i> | 1 (0.5%)  | 1 (0.5%)   |
| <i>Pruritus</i>                 | -   | 2 (1.0%)   |
| <i>Abdominal pain</i>           | 1 (0.5%)  | -  |
| <i>Anal discomfort</i>          | -   | 1 (0.5%)   |
| <i>Back pain</i>                | -   | 1 (0.5%)   |
| <i>Defaecation urgency</i>      | -   | 1 (0.5%)   |
| <i>Flatulence</i>               | -   | 1 (0.5%)   |
| <i>Nausea</i>                   | 1 (0.5%)  | -  |

The following adverse events presented by body system have been reported in international post marketing surveillance of all SALOFALK preparations. In many cases, the relationship to SALOFALK has not been established.

The **common: (≥1% - <10%) adverse events** were as follows:

***Body as a whole – General Disorders***

Headache

***Gastrointestinal***

Abdominal pain, diarrhoea, nausea and vomiting, flatulence, exacerbation of ulcerative colitis

***Skin and Appendages Disorder***

Rash including pruritus, urticaria

The following additional adverse reactions were **uncommon and reported by < 1% of patients**:

***Body as a Whole – General Disorders***

Fever, allergic reaction

***Central and Peripheral Nervous Systems Disorders***

Dizziness, paraesthesia, peripheral neuropathy

***Collagen disorders***

Lupus erythematosus syndrome (as observed for preparations with a similar chemical structure).

**Gastrointestinal System Disorders**

Acute pancreatitis, pancolitis, neonate diarrhoea

**Liver and Biliary System Disorders**

Hepatitis, increased liver enzyme values (transaminase activity), intrahepatic cholestasis, increased bilirubin

**Musculo-skeletal System Disorders**

Arthralgia, myalgia, myositis

**Myo-, Endo-, Pericardial and Valve Disorders**

Pericarditis, myocarditis, pericardial effusion

**Platelet, Bleeding and Clotting Disorders**

Thrombocytopenia

**Red Blood Cell Disorders**

Aplastic anaemia, haemolytic anaemia

**Reproductive System Disorders**

Oligospermia (reversible)

**Respiratory System Disorders**

Bronchospasm, pleural effusion, alveolitis (In isolated cases hypersensitivity reactions, principally in the form of respiratory problems, may be experienced by non-asthmatics due to the content of sodium metabisulfite in enemas.)

**Skin and Appendages Disorders**

Alopecia, allergic exanthema, increased sweating

**Urinary System Disorders**

Acute or chronic interstitial nephritis, renal insufficiency, renal failure, nephrotoxicity

**White Cell and RES Disorders**

Agranulocytosis, leukopenia, neutropenia, pancytopenia

**DOSAGE AND ADMINISTRATION**

One SALOFALK 1 g suppository should be inserted into the rectum once daily at bedtime. The best results are achieved if the bowels are evacuated prior to insertion of SALOFALK suppository.

**Use in Children**

SALOFALK enemas should not be used in children 12 years old and under, as there is little experience with this age group.

## **OVERDOSAGE**

No overdosage has been reported to date. Possible symptoms may include nausea, vomiting and diarrhoea, and symptoms similar to salicylate overdose.

There is no specific antidote. General supportive and symptomatic measures are recommended. For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

## **PRESENTATION**

SALOFALK moulded suppositories are presented as light beige coloured, torpedo-shaped suppositories in white plastic strip packs.

Each SALOFALK 1 g suppository contains 1 g of mesalazine. Cartons of 5\* and 30 suppositories are available. (\*currently not marketed)

## **STORAGE CONDITIONS**

Store below 25°C. Protect from light.

## **NAME AND ADDRESS OF THE SPONSOR**

Orphan Australia Pty. Ltd.  
300 Frankston-Dandenong Road  
Dandenong  
Victoria 3175  
Australia.

## **POISON SCHEDULE OF THE MEDICINE**

S4

## **DATE OF APPROVAL**

This Product Information was approved by the TGA on: 6 May 2010  
Date of most recent amendment: 20 October 2010

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