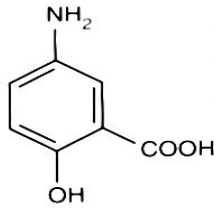


## PRODUCT INFORMATION

### SALOFALK® Enemas

#### 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 enemas contain, mesalazine, carbomer 934, disodium edetate, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum. The disposable unit consists of an applicator tip protected by a polyethylene cover and lubricated with white petrolatum. The unit has a one-way valve to prevent back flow of the dispensed product.

#### 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 enemas.

#### **SALOFALK enemas:**

4g/60 mL enema in patients with ulcerative colitis in remission show a median  $C_{max}$  value of 0.92 µg/mL for 5-ASA at  $t_{max}$  of 11 hours, and for N-acetyl-5-ASA a median  $C_{max}$  of 1.62 µg/mL at a  $t_{max}$  of 12 hours. The median urinary recovery was 13% during 45 hours, indicating a low absorption.

The administration of high doses of mesalazine enema (2xSALOFALK 4g/60 mL daily) in patients with severely active ulcerative colitis, instilled into the caecum, showed the following  $C_{max}$  values in plasma for 5-ASA at  $t_{max}$  of 1.5 h and for N-acetyl-5-ASA at  $t_{max}$  of 2.8 h.

Application Day	5-ASA [µg/mL]	N-acetyl-5-ASA [µg/mL]
1	1.4	1.9
2	2.5	3.6

Total urinary recovery on day 1 was 10.5% and on day 3 (steady state) 18.6% with 22% of that being 5-ASA, demonstrating, like with the oral application of SALOFALK granules, a low absorption rate. The serum elimination half-life on day 1 was 4.2h, therefore comparable with that of the SALOFALK granules (4.4h).

In children with ulcerative colitis, SALOFALK enemas showed the following steady state plasma concentrations:

SALOFALK enema	5-ASA [µg/mL]	Ac-5-ASA [µg/mL]
2g/30 mL	0.2 - 1.0	0.4 - 2.0
4g/60 mL	0.5 - 2.8	0.9 - 4.1

Scintigraphic evaluation of (<sup>99</sup>Tc) technecium-sulphur colloid-labelled SALOFALK 2g /30 mL and SALOFALK 4 g/60 mL enema showed the following distribution in patients with mild to moderate active ulcerative colitis at the beginning of therapy (time: 0 week) and at time of remission after 12 weeks of treatment (median and range):

Distribution Region	SALOFALK 2g/30 mL		SALOFALK 4g/60 mL	
	0 week [%]	12 week [%]	0 week [%]	12 week [%]
Rectum	1 (0-76)	0 (0-21)	9 (0-77)	3 (0-51)
Sigmoid	99 (13-100)	100 (51-100)	61 (23-100)	85 (47-100)
Descending colon	0 (0-47)	0 (0-35)	13 (0-68)	0 (0-51)
Transverse colon	0 (0-39)	0 (0-5)	0 (0-0)	0 (0-0)
Ascending colon	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

## **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, mucosal appearance on endoscopy, and severity of the disease as evaluated by a physician. These criteria have been summarised in the disease activity index (DAI) to evaluate the efficacy of treatment for ulcerative colitis. In a multi-centre, randomised, double-blind, placebo-controlled study involving 153 patients, the efficacy of SALOFALK 4g/60 mL enemas in the therapy of

ulcerative colitis was significantly better than that of placebo at 6 weeks. The study showed an endoscopic improvement of 70% vs. 37% of placebo (p=0.001). It also showed a 63% improvement by the physician global assessment (PGA) in the mesalazine group vs. 29% in the placebo group (p<0.001) while evaluation by the DAI showed a 55% decline (7.42 to 3.37) in the 5-ASA group vs. 22% (7.7 to 5.83) in the placebo group (p=0.0001). All components of the DAI were significantly lower for the treatment group than the placebo group, see table below.

Primary Efficacy Criteria, 4g/60 mL Enema Vs Placebo						
Efficacy Parameter	Treatment group	Mean Observation				Change from Baseline to Endpoint
		Baseline	Day 22	Day 43	Endpoint	
Overall Disease Activity Index	5-ASA	7.42	4.05**	2.67***	3.37***	-55.07%+***
	Placebo	7.70	6.03	5.07	5.83	-21.53%
a) Stool Frequency Index	5-ASA	1.53	1.11*	0.94*	1.01**	-0.57
	Placebo	1.92	1.47	1.31	1.50	-0.41
b) Rectal Bleeding Index	5-ASA	1.82	0.59***	0.34***	0.51***	-1.30***
	Placebo	1.73	1.21	0.87	1.11	-0.61
c) Mucosal Appearance Index	5-ASA	2.17	1.22**	0.79***	0.96***	-1.21***
	Placebo	2.13	1.74	1.44	1.61	-0.56
d) Physician Assessment of Disease Severity	5-ASA	1.86	1.13***	0.70***	0.88***	-0.97***
	Placebo	1.87	1.62	1.39	1.55	-0.30

- + Percent change for overall DAI only
- \* Significant 5-ASA / Placebo difference, p<0.05
- \*\* Significant 5-ASA / Placebo difference, p<0.01
- \*\*\* Significant 5-ASA / Placebo difference, p<0.001

On completing the above study, patients were randomised to receive once daily SALOFALK 4g/60 mL or 2g/60 mL. This open study, showed the DAI score decreased by 62-75 % after 6 months of therapy, and there was no significant difference in the degree of improvement between the groups. A dose-dependent relationship with mesalazine does not seem to be evident in the maintenance of remission.

## INDICATIONS

SALOFALK enemas are indicated in the treatment of acute ulcerative colitis of mild to moderate severity and for the maintenance treatment of ulcerative colitis.

## CONTRAINDICATIONS

SALOFALK enema is contraindicated in patients with the following:

- hypersensitivity to salicylic acid, salicylic acid derivatives, e.g. mesalazine/5-ASA, sulfites and benzoates or to any of the other ingredients
- severe impairment of hepatic and renal function

SALOFALK enemas should be used with caution in patients with bronchial asthma. They contain sulfite which may cause hypersensitivity reactions.

## 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 is 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, which is less than the maximal recommended clinical dose of SALOFALK enemas 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, representing less than, and about twice, the maximal recommended clinical dose of SALOFALK enemas on a body surface area basis. Oral mesalazine does not show 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 a neonate was reported.

SALOFALK enemas 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, which is less than the maximal recommended clinical dose of SALOFALK enemas 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 enemas in lactating women. SALOFALK enemas should not be used during lactation unless the likely benefit of treatment outweighs the potential hazard.

### **Paediatric use**

SALOFALK enemas 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 1 and 6 fold the respective clinical plasma concentrations associated with a 1500 mg dose of the granules and the 4 g/60mL enema.

### **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.

There is growing information that 5-ASA/mesalazine protects patients with ulcerative colitis from colo-rectal cancer.

## Interactions with other medicines

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

The most common adverse events seen in clinical study are headache, hair loss, abdominal pain, diarrhoea and rash. In a placebo controlled clinical trial involving 153 patients, adverse events occurred in 25% and 40% of patients in the mesalazine and placebo enema groups respectively. Events reported by at least 2 patients in this trial are shown in Table I below.

Table I

System/reaction	Salofalk 4g/60mL enema (n=76)	Placebo (n=77)
<b>Body as a whole-General Disorders</b>		
Headache	11.8%	7.8%
Cold	1.3%	9.1%
Fatigue	2.6%	6.5%
Hair loss	2.6%	0%
<b>Gastrointestinal</b>		
Nausea	0%	6.5%
Bloating	2.6%	2.6%
Constipation	1.3%	2.6%
Diarrhoea	2.6%	1.3%
Cramps	1.3%	3.9%
<b>Skin and Appendages Disorder</b>		
Rash	2.6%	5.2%
<b>Cardiovascular</b>		
Dizziness	0%	2.6%
<b>Genitourinary</b>		
Urinary tract infection	0%	2.6%
<b>Psychiatric</b>		
Insomnia	1.3%	2.6%

The following adverse events presented by body system have been reported in international post marketing surveillance of SALOFALK preparations including enemas and tablets. 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 System Disorders**

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

**Skin and Appendages Disorder**

Rash including pruritus, urticaria

The following additional adverse events 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 potassium bisulfite 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**

Unless otherwise advised a dose of 2g or 4g mesalazine as SALOFALK enema once a day is used for the treatment of acute ulcerative colitis or maintenance of remission.

The content of one enema bottle (2 g/30 mL, 2 g/60 mL, or 4 g/60 mL) is instilled in the rectum once every evening prior to going to bed.

The best results are achieved if the bowels are evacuated prior to instillation of SALOFALK enema. The action of SALOFALK is enhanced if the patient lies on the left side when introducing the enema. The dosage should be adjusted to suit the progress of the condition.

Discontinuation of treatment should be under supervision of the physician. Due to the considerable variation in the severity of the ulcerative colitis and the extent of the affected area it is not possible to recommend a uniform dose of mesalazine which will provide optimal effects. In clinical trials, rectal doses of 2-4 g mesalazine/day as enemas have been used in the therapy of both acute ulcerative colitis and maintenance of remission.

**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 enemas**, 2 g/30 mL, 2 g/ 60 mL and 4 g/60 mL, are presented as a very light tan to brown, homogeneous suspension. They are supplied in opaque low-density concertina shaped polyethylene squeeze bottles with a low-density polyethylene applicator nozzle in cardboard cartons.

Each carton contains 7 enemas in individual blister packs.

## 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

SALOFALK® is a registered trademark of Dr. Falk Pharma GmbH, Germany, used under licence by Orphan Australia Pty. Ltd.