

AUSTRALIAN PRODUCT INFORMATION

SALOFALK[®] Suppositories (mesalazine)

1. NAME OF THE MEDICINE

Mesalazine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALOFALK suppositories contain 1 g mesalazine as the active ingredient.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SALOFALK suppositories are light beige coloured, torpedo-shaped suppositories.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SALOFALK suppositories are indicated in the treatment of ulcerative proctitis.

4.2 DOSE AND METHOD OF 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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SALOFALK should be given/used under medical supervision.

Use in pulmonary function impairment

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.

Use in hepatic impairment

Caution is recommended in patients with impaired hepatic function. SALOFALK suppositories are contraindicated in patients with severe hepatic impairment (see Section 4.3 Contraindications).

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, γ 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.

Use in renal impairment

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.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with mesalazine content. Ensure adequate fluid intake during treatment.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including 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 reaction, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.

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.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

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

Adverse Event	Salofalk 1 g suppositories (n=200)	Salofalk 500 mg suppositories (n=203)
Constipation	2 (1.0%)	1 (0.5%)
Lipase increased	1 (0.5%)	1 (0.5%)
Platelet count decreased	1 (0.5%)	1 (0.5%)
Pruritus	-	2 (1.0%)
Abdominal pain	1 (0.5%)	-
Anal discomfort	-	1 (0.5%)
Back pain	-	1 (0.5%)
Defaecation urgency	-	1 (0.5%)
Flatulence	-	1 (0.5%)
Nausea	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: ($\geq 1\%$ - $< 10\%$) 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, Thoracic and Mediastinal Disorders

Allergic and fibrotic lung reactions, dyspnoea, cough, bronchospasm, pleural effusion, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis (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

The following additional adverse events were **rare and reported by < 0.1% of patients:**

Skin and appendages disorders

Photosensitivity

(More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema)

The following additional adverse events were **very rare and reported by < 0.01% of patients**:

Liver and biliary system disorders

Cholestatic hepatitis

The frequency of the following adverse events is **not known**:

Urinary System Disorders

Nephrolithiasis (see section 4.4 Special Warnings and Precautions for Use for further information)

Skin and subcutaneous tissue disorders SOC

Stevens-Johnson-syndrome (SJS), toxic epidermal necrolysis (TEN)

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

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.

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 information on the management of overdosage, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

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 ^a [95% CI]	Shifted asymptotic χ^2 test for comparing two rates ^b
		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 ^c
	ITT	168/200 (84.0%)	172/203 (84.7%)	-0.7% [-7.8%, 6.4%]	3.790 ^c

OD, once daily; TID, three times daily

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

^b 'Effect' = difference between proportions [Salofalk 1 g suppository OD – Salofalk 500 mg suppository TID] + 0.15)

^c 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 ^a		CAI		EI ^b	
	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 n = 182	TID n = 172	OD n = 182	TID n = 172	OD n = 176	TID 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

^a Patients with (DAI) > 3 at baseline.

^b 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.

5.2 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.

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

Absorption

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.

SALOFALK suppositories:

The mean peak plasma concentrations of mesalazine after a single rectal dose of 1 g mesalazine (SALOFALK 1 g suppository) were 192 ± 125 ng/mL (range 19 – 557 ng/mL), those of the main metabolite N-Acetyl-5-ASA were 402 ± 211 ng/mL (range 57 – 1070 ng/mL). Time to reach the peak plasma concentration of mesalazine was

7.1 ± 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

Distribution

The plasma protein binding of mesalazine and acetylated mesalazine is 43% and 78%, respectively.

SALOFALK suppositories:

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.

Metabolism

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.

Excretion

Absorbed mesalazine and N-acetyl-5-ASA are eliminated mainly via kidneys. Biliary excretion is a minor route of elimination.

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.

5.3 PRECLINICAL SAFETY DATA

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.

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_{max} concentrations associated with a 1 g dose of SALOFALK suppository.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SALOFALK suppositories contain the excipient hard fat.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

SALOFALK 1 g moulded suppositories are available in white PVC/PE strip packs. Pack sizes of 5 and 30 suppositories.

Not all pack sizes are currently available in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

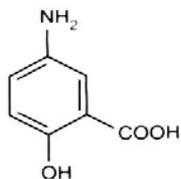
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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).

Proper name: 5-Aminosalicylic Acid, chemical name: 2-hydroxy-5-aminobenzoic acid, also referred to as 5-amino salicylic acid or 5-ASA. $C_7H_7NO_3 = 153.1$

Chemical structure



CAS number

89-57-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Dr Falk Pharma Australia Pty Ltd
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Chatswood, NSW 2067
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9. DATE OF FIRST APPROVAL

24 May 2010

10. DATE OF REVISION

23 December 2020

SALOFALK® is a registered trademark of Dr. Falk Pharma GmbH, Germany.

Summary table of changes

Section changed	Summary of new information
Heading	Trade name harmonized in document heading.
8	Sponsor details updated (MAH transfer).
4.4 / 4.8	Additional safety related information relating to “Nephrolithiasis”, Stevens-Johnson syndrome and Toxic epidermal necrolysis