

AUSTRALIAN PRODUCT INFORMATION

SALOFALK[®] Suppositories (mesalazine)

1. NAME OF THE MEDICINE

SALOFALK mesalazine 1 g suppository

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 the SALOFALK suppository.

Use in Children

SALOFALK suppositories 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 the 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

Mesalazine 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 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.

Blood dyscrasia

Serious blood dyscrasias have been reported very rarely with mesalazine. Haematological investigations should be performed if patients suffer from unexplained haemorrhages, bruises, purpura, anaemia, fever or pharyngolaryngeal pain. SALOFALK should be discontinued in case of suspected or confirmed blood dyscrasia.

Epigastric pain

Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or sulfasalazine therapy, should be investigated in order to exclude conditions such as pericarditis, hepatitis and pancreatitis either as adverse drug reactions to mesalazine or secondary manifestations of inflammatory bowel disease. Cardiac hypersensitivity reactions (myocarditis, and pericarditis) induced by mesalazine have been rarely reported. SALOFALK should then be discontinued immediately if any of these reactions occur.

Use in renal impairment

Mesalazine 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 performing a urine sediment test. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment. If this is the case, SALOFALK should be discontinued immediately.

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 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 reaction, 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.

Urine discoloration

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).

Use in the elderly

Specific clinical data in only elderly patients for mesalazine are not available but mesalazine has 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 suppositories 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

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 3rd and 5th 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 suppositories should not be used during lactation unless the likely benefit of treatment outweighs the potential risk. If the infant develops diarrhoea, the treatment should be temporarily discontinued and further medical advice sought.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Mesalazine is 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 once daily (n=200)	SALOFALK 500 mg suppositories TID (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, including SALOFALK suppositories. In many cases, the relationship to SALOFALK treatment 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, constipation, exacerbation of ulcerative colitis

Skin and Appendages Disorder

Rash including pruritus, urticaria

The following additional adverse reactions were classified as **uncommon being reported in $< 1\%$ 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, changes in pancreatic enzymes (lipase and amylase increased), eosinophil count increased

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 classified as **rare being reported in < 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 classified as **very rare being reported in < 0.01% of patients:**

Liver and biliary system disorders

Cholestatic hepatitis

The frequency of the following adverse events is **not known** (i.e. cannot be estimated from the available data):

Urinary System Disorders

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

Skin and subcutaneous tissue disorders SOC

Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson-syndrome (SJS), toxic epidermal necrolysis (TEN)

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).

Nervous system disorders

Idiopathic intracranial hypertension (see section 4.4)

4.9 OVERDOSE

There are limited 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 administered once daily at bedtime in the therapy of acute ulcerative proctitis was demonstrated to be therapeutically equivalent to that of SALOFALK 500 mg suppository administered 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 500 mg Suppository		
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 500 mg Suppository	SALOFALK 1 g Suppository	SALOFALK 500 mg Suppository	SALOFALK 1 g Suppository	SALOFALK 500 mg 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

The systemic absorption of mesalazine decreases in the intestinal tract from proximal to distal segments. Because of low systemic absorption rates from oral delayed release preparations or rectal applications forms of mesalazine, 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) was 192 ± 125 ng/mL (range 19 – 557 ng/mL), while for the main metabolite N-Acetyl-5-ASA it was 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 mesalazine levels following rectal administration are lower than those following oral administration.

Pharmacokinetic data are summarised in the following table for SALOFALK 1 g suppositories administered 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 mesalazine after 2 -3 hours following the melting of the suppository due to body temperature. The spread of the mesalazine 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 similar to mesalazine is 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

Systemically 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 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 1 g 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

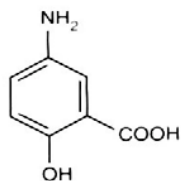
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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

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9. DATE OF FIRST APPROVAL

24 May 2010

10. DATE OF REVISION

01 May 2025

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

Summary table of changes

Section changed	Summary of new information
4.4, 4.8	Addition of idiopathic intracranial hypertension
4.4, 4.9	Minor editorial changes for readability