AUSTRALIAN PRODUCT INFORMATION

SALOFALK® foam (mesalazine)

1 NAME OF THE MEDICINE

Mesalazine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SALOFALK foam contains 1 g/application mesalazine as the active ingredient.

Excipients with known effect: sulphites

See section 4.4 Special warnings and precautions for use

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

3 PHARMACEUTICAL FORM

SALOFALK foam is a white-greyish to slightly reddish violet, creamy firm foam.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

A dose of 2 g SALOFALK foam is equivalent to 2 applications.

SALOFALK foam should be used at room temperature, 20 – 25°C (please also see section 6.4 Special Precautions for Storage). The canister is first fitted with an applicator and then shaken for about 15 seconds before the applicator is inserted into the rectum as far as comfortable. To administer a dose of SALOFALK foam, the pump dome is fully pushed down and released. Note the spray can will only work properly when held with the pump dome pointing down. Following the second activation, the applicator should be held in position for 10-15 seconds before being withdrawn from the rectum. The best results are achieved if the bowels are evacuated prior to instillation of SALOFALK foam. 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 foam have been used in the therapy of both acute ulcerative colitis and maintenance of remission.

Use in Children

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

4.3 CONTRAINDICATIONS

SALOFALK foam is contraindicated in patients with the following:

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SALOFALK foam should be given/used under medical supervision.

Use in pulmonary function impairment
SALOFALK foam 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 foam is 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, γGT) 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 reactions, 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 foam 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.

Excipients with known effect
This medicine contains propylene glycol that may cause lactic acidosis, hyperosmolality, haemolysis and CNS depression. Care should be taken when administering SALOFALK foam to patients with diminished renal function. Slight to mild skin irritation due to propylene glycol may occur.

This medicine contains cetostearyl alcohol that may cause local skin reactions (e.g. contact dermatitis).

Salofalk foam also contains sodium metabisulfite. In isolated cases hypersensitivity reactions principally in the form of respiratory problems may be experienced also by non-asthmatics due to the content of sulphite.

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 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, which is less than the maximal recommended clinical dose of SALOFALK foam 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 foam 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.

No animal studies with SALOFALK foam have been performed.

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 foam 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 foam 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 foam in lactating women. SALOFALK foam should not be used during lactation unless the likely benefit of treatment outweighs the potential hazard.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SALOFALK foam is generally not expected to affect the ability of patients to drive or operate machinery. However, as SALOFALK foam may cause dizziness, patients should be cautioned about their ability to drive a car and 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.

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 111 patients, the rate of patients reporting at least 1 adverse event is 29.6% and 42.1% in the mesalazine and

placebo foam groups respectively. The absolute and relative frequencies of patients with adverse events by Body System are shown in Table I below.

Table I

System/reaction	***Salofalk 2g/ day foam (n=54)***	***Placebo (n=57)***
Gastrointestinal system	*6 (1.1%)*	*14 (24.6%)*
Respiratory system	*4 (7.4%)*	*5 (8.8%)*
Body as a whole-General disorders	*3 (5.6%)*	*6 (10.5%)*
Central and peripheral nervous system	*5 (9.3%)*	*4 (7.0%)*
Haematologic/Lymphatic system	*2 (3.7%)*	*8 (14.0 %)*
Reproductive, female	*1 (1.9%)*	*1 (1.8%)*
Metabolic and nutritional	-	*2 (3.5%)*
Skin and appendages	-	*1 (1.8%)*
Musculo-skeletal system	-	*1 (1.8%)*
Application site disorders	-	*1 (1.8%)*

The following adverse events presented by body system have been reported in international post marketing surveillance of SALOFALK preparations including foam, 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 and Administration Site Conditions
Headache, abdominal distension

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 reactions were **uncommon and reported by < 1% of patients**:

Body as a Whole – General Disorders and Administration Site Conditions
Fever, allergic reaction, anal discomfort, application site irritation, painful rectal tenesmus

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).

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)

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 wellbeing, temperature, extra intestinal manifestations, 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, double blind, placebo-controlled study (SAF-4/UCA) involving 111 patients, the efficacy of SALOFALK 2g/60 mL foam in the therapy of ulcerative colitis was significantly better than that of placebo at 6 weeks. The response rate was 64.8% vs. 40.4% placebo (p=0.0082). The study showed an endoscopic improvement of 70.4 vs. 45.6 % in the placebo group.

Results of the studies and post marketing reports show that SALOFALK foam is well tolerated in patients with ulcerative colitis.

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.

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.

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

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.

SALOFALK foam:
In an open, randomised, cross-over study, healthy volunteers were given 7 doses of SALOFALK foam each dose consisting of 2 applicatorfuls equivalent to 2g mesalazine per day. The C_{max} values after the first and last dose (steady state, 7 doses) are 985.1 ng/mL at t_{max} of 2.3 h and 774.9 ng/mL at t_{max} of 2.4 h, respectively. A summary of the pharmacokinetic data is presented below:

Pharmacokinetic parameters in healthy subjects	Salofalk foam (single dose of 2 applicatorfuls per day)	
	Mesalazine Mean [SD]	N-Acetyl-5-ASA Mean [SD]
After Dose 1		
C_{max} [ng/mL]	985.1 [682.4]	1216.1 [649.1]
t_{max} [hr]	2.3 [1.3]	2.9 [1.0]
$t_{1/2}$ [hr]	2.4 [2.0]	4.3 [3.2]
$AUC_{(0-\infty)}$ [hr*ng/mL]	3794.3 [2568.2]	8462.1 [6025.8]
Ae_{0-48h} [mg]	2.1 [1.8]	136.7 [121.0]
After Dose 7 (Steady State)		
C_{max} [ng/mL]	774.9 [434.5]	955.0 [365.4]
t_{max} [hr]	2.4 [1.1]	3.1 [1.7]
$t_{1/2}$ [hr]	5.5 [4.8]	3.6 [1.9]
$AUC_{(0-\infty)}$ [hr*ng/mL]	3541.0 [2730.4]	6738.3 [3938.0]
Ae_{0-48h} [mg]	4.7 [6.5]	138.8 [111.2]

In an open, non-randomised, single dose study, patients with active ulcerative proctitis or proctosigmoiditis were administered a single dose of foam consisting of 2

applicatorfuls, equivalent to 2 g mesalazine. Results showed a C_{max} value of 1661.3 ng/mL for 5-ASA at t_{max} of 1.3 hour, and for N-acetyl-5-ASA a median C_{max} of 1579.3 ng/mL at a t_{max} of 2.4 hours. The urinary recovery of 5-ASA + N- acetyl-5-ASA within 48 hours after single dose application of 2g mesalazine was 5.5%. Pharmacokinetic data for SALOFALK foam in patients with active ulcerative proctitis or protosigmoiditis are summarised in the following table:

Pharmacokinetic parameters in patients	Salofalk foam (single dose of 2 applicatorfuls)	
	Mesalazine Mean [SD]	N-Acetyl-5-ASA Mean [SD]
C_{max} [ng/mL]	1661.3 [1238.4]	1579.3 [948.3]
t_{max} [hr]	1.3 [1.0]	2.4 [0.9]
$t_{1/2}$ [hr]	1.6 [1.1]	2.6 [1.6]
$AUC_{(0-\infty)}$ [hr*ng/mL]	5285.1 [3325.9]	7967.0 [4412.4]
Ae_{0-48h} [µMol]	79.3 [105.2]	812.3 [465.6]

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

Scintigraphic evaluation of samarium(^{153}Sm) labelled SALOFALK foam versus SALOFALK enema showed that there is no significant difference in the rectal spread and intestinal distribution between the two dosage forms. The tables below show the rectal and intestinal distribution of SALOFALK foam versus SALOFALK enema in patients with left-sided ulcerative colitis and healthy subjects.

The rectal and intestinal distribution of SALOFALK foam and SALOFALK enema in healthy subjects:

Distribution Region	Salofalk foam 2 g dose		Salofalk enema 2 g/60 mL	
	5 min [% of total dose]	12 hours [% of total dose]	5 min [% of total dose]	12 hours [% of total dose]
Ascending colon	0	0	0	0
Transverse colon	0	0	0	0
Descending colon	0	7.00	0	8.50
Sigmoid	28.50	28.50	18.17	29.83
Rectum	46.25	39.50	81.83	28.33

The rectal and intestinal distribution of SALOFALK foam and SALOFALK enema in patients with left-sided ulcerative colitis:

Distribution Region	Salofalk foam 2g dose		Salofalk enema 2g/60 mL	
	5 min [% of total dose]	12 hours [% of total dose]	5 min [% of total dose]	12 hours [% of total dose]
Ascending colon	0	0	0	0
Transverse colon	0	0	0	0
Descending colon	0	5.00	0	5.17
Sigmoid	33.60	22.20	30.00	11.67
Rectum	66.40	52.80	70.00	66.50

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SALOFALK foam contains sodium metabisulfite, polysorbate 60, cetostearyl alcohol, disodium edetate, propylene glycol, propane, butane and isobutane.

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. Do not refrigerate or freeze.

This is a pressurised container, containing 3.75% by mass of flammable propellant. It should be kept away from any flames or sparks, including cigarettes. It should be protected from direct sunlight and must not be pierced or burnt even when empty. Do not refrigerate or freeze. Actuated containers should be used up within 12 weeks.

6.5 NATURE AND CONTENTS OF CONTAINER

SALOFALK foam is available in an aluminium pressurised container with a metering valve containing 80 g of foam and 14 disposable PVC applicators for the administration of the foam. The disposable unit consists of an applicator tip protected by a polyethylene tray and lubricated with white soft paraffin and liquid paraffin. The unit has a one-way valve to prevent back flow of the dispensed product. Each can contains sufficient foam for 14 applications (equivalent to 7 doses of 2 g mesalazine).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

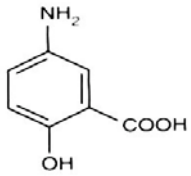
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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

8. SPONSOR

Dr Falk Pharma Australia Pty Ltd
815 Pacific Highway
Chatswood, NSW 2067

Phone: 1800 DRFALK (373 255)

9. DATE OF FIRST APPROVAL

5 October 2004

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
4.4 / 4.8	Additional safety related information relating to "Nephrolithiasis", Stevens-Johnson syndrome and Toxic epidermal necrolysis.
4.4	Addition of ingredients warning: cetostearyl alcohol and sodium metabisulfite.
2	Addition of excipient of known effect: sulphites
Heading,	Trade name harmonized in document heading.
8	Sponsor details updated (MAH transfer).
All	Change of product name throughout PI to remove incorrect dosage form enema.