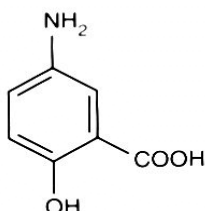


PRODUCT INFORMATION**SALOFALK[®] foam enemas****NAME OF DRUG****Mesalazine**

Proper name: 5-Aminosalicylic Acid

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

C₇H₇NO₃ = 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 foam enemas contain, mesalazine, sodium metabisulfite, polysorbate 60, cetostearyl alcohol, disodium edetate, propylene glycol, propane, n-butane and isobutane.

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 lipooxygenase 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.

In an open, randomised, cross-over study, healthy volunteers were given 7 doses of SALOFALK foam enema 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 enema (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 enema 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 enema in patients with active ulcerative proctitis or proctosigmoiditis are summarised in the following table:

Pharmacokinetic parameters in patients	Salofalk foam enema (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-∞) [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 enemas.

Scintigraphic evaluation of samarium(¹⁵³Sm) 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 enema versus SALOFALK enema in patients with left-sided ulcerative colitis and healthy subjects.

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

Distribution Region	Salofalk foam enema 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	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 enema and SALOFALK enema in patients with left-sided ulcerative colitis:

Distribution Region	Salofalk foam enema 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

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, 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.

INDICATIONS

SALOFALK foam 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 foam enemas are 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 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, 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.

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.

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.

SALOFALK foam enema is generally not expected to affect the ability of patients to drive or operate machinery. However, as Salofalk may cause dizziness, patients should be cautioned about their ability to drive a car and 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 3rd and 5th months of pregnancy, renal failure in the 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 foam 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 foam enemas in lactating women. SALOFALK should not be used during lactation unless the likely benefit of treatment outweighs the potential hazard.

Paediatric use

SALOFALK foam 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.

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 111 patients, the rate of patients reporting at least 1 adverse event is 29.6% and 42.1% in the mesalazine and placebo foam enema 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 enema (n=54)	Placebo (n=57)
<i>Gastrointestinal system</i>	6 (1.1%)	14 (24.6%)
<i>Respiratory system</i>	4 (7.4%)	5 (8.8%)
<i>Body as a whole-General disorders</i>	3 (5.6%)	6 (10.5%)
<i>Central and peripheral nervous system</i>	5 (9.3%)	4 (7.0%)
<i>Haematologic/Lymphatic system</i>	2 (3.7%)	8 (14.0 %)
<i>Reproductive, female</i>	1 (1.9%)	1 (1.8%)
<i>Metabolic and nutritional</i>	-	2 (3.5%)
<i>Skin and appendages</i>	-	1 (1.8%)
<i>Musculo-skeletal system</i>	-	1 (1.8%)
<i>Application site disorders</i>	-	1 (1.8%)

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 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

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

A dose of 2g SALOFALK foam is equivalent to 2 applications. 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 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 foam 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 foam enemas are available in an aluminium pressurised container with a metering valve containing 80 g of foam and 7 disposable applicators for the administration of the foam. 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. Each can contains sufficient foam for 14 applications (equivalent to 7 doses of 2g mesalazine). SALOFALK foam is presented as a white greyish to slightly reddish violet, creamy firm foam.

STORAGE CONDITIONS

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.

NAME AND ADDRESS OF THE SPONSOR

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

POISON SCHEDULE OF THE MEDICINE

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DATE OF APPROVAL

This Product Information was approved by the TGA on: 6 May 2010

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