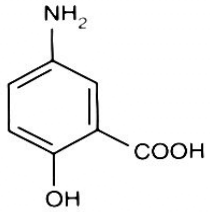
PRODUCT INFORMATION

SALOFALK® Granules

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 granules have a functional coating on the particles, which ensures gastro-resistance to allow a reliable distribution and pH-dependent release of the active ingredient, mesalazine, at the intended site of action starting in the ileocoecal region. The granules also contain a matrix system inside the particle core, which releases mesalazine independently of pH.

SALOFALK granules contain mesalazine, microcrystalline cellulose, hypromellose, anhydrous colloidal silica, methacrylic acid copolymer, nonoxinol 100, magnesium stearate, simethicone emulsion (containing sorbic acid and methylcellulose), triethyl citrate, purified talc, carmellose sodium, aspartame, anhydrous citric acid, vanilla custard flavour 75016-32 (containing propylene glycol), povidone, titanium dioxide.

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. Less than 1% 5-ASA and about 24% N-acetyl-5-ASA based on the administered 5-ASA dose are excreted in the urine. Biliary excretion is a minor route of elimination.

There is no pharmacokinetic data in the elderly using SALOFALK granules or tablets.

SALOFALK granules:
SALOFALK granules are gastric juice resistant and release mesalazine in the terminal ileal region in a pH dependent manner due to the Eudragit-L coating. The release of mesalazine from the granules is prolonged due to the matrix granule structure. Owing to the granule size, under starved condition transit from the stomach to the small intestine is fast (0.65 + 0.40 hours). For the granules food intake may cause a shift of 1 to 2 hours to a longer t_{lag} value (lag time after which mesalazine concentrations are first detectable in blood plasma) and a longer t_{max} value, but does not cause dose-dumping due to the small granule size. Food does cause a slight increase in C_{max} and AUC values.

Pharmacokinetic data are summarised in the following table for SALOFALK granules and tablets (granules: 3 x 500 mg mesalazine/day, tablets: 3 x 2 (250mg) mesalazine/day, steady state conditions, 24 healthy volunteers):

	Granules		Tablets	
Pharmacokinetic Parameters	Mesalazine/5-ASA	N-Acetyl-5-ASA	Mesalazine/5-ASA	N-Acetyl-5-ASA
t_{lag} [h]	2.4 ± 0.8	2.4 ± 0.8	3.4 ± 1.0	3.5 ± 0.9
t_{max} [h]	4.3 ± 0.6	4.5 ± 0.9	4.4 ± 0.9	4.6 ± 0.9
$t_{1/2}$ [h]	4.4 ± 3.9	8.2 ± 6.0	2.8 ± 1.9	5.0 ± 2.4
C_{max} [µg/mL]	0.8 ± 0.4	1.8 ± 0.7	2.0 ± 1.5	2.6 ± 1.4
AUC_{0-24h} [µg x h/mL]	7.7 ± 3.3	29.0 ± 7.5	12.2 ± 6.4	34 ± 10.7
A_e urine [mmol]	0.286 ± 0.28	9.4 ± 2.4	1.48 ± 1.0	10.98 ± 2.8
A_e urine [%]	0.72 ± 0.7	24.03 ± 6.2	3.77 ± 2.5	28.02 ± 7.0
$\sum A_e$ 5-ASA + Ac-5-ASA [mmol]	9.7 ± 2.6		12.5 ± 3.4	
$\sum A_e$ 5-ASA + Ac-5-ASA [%]	24.8 ± 6.5		31.8 ± 8.8	

The total quantity of mesalazine and N-acetyl-5-ASA eliminated by the renal pathway over 24 hours is equivalent to about 25% to 32% respectively of the administered dose of SALOFALK granules and tablets. About 30% of this amount is absorbed in the ileocoecal area and about 90% in total in the ileocoecal and ascending colon regions. Therefore about 80-90% 5-ASA of administered dose is available in the descending colon, sigmoid and rectum where absorption of mesalazine is low.

Granule and tablet preparations radio-labelled with ^{153}Sm (Samarium) showed the following gastrointestinal distribution (means ± S.D.):

	Granules	*Tablets*
Gastric emptying	0.94 ± 0.70 h	0.56 ± 0.71 h
Appearance in small bowel	0.65 ± 0.40 h	0.79 ± 0.71 h
Transit time in small bowel	3.07 ± 0.88 h	3.00 ± 0.84 h
Disappearance from small bowel	3.71 ± 1.08 h	3.79 ± 1.17 h
Ileocoecal region: appearance	3.31 ± 1.03 h	3.83 ± 0.89 h
Ileocoecal region: disappearance	6.15 ± 2.48 h	5.56 ± 1.57 h
Ascending colon: appearance	4.08 ± 1.39 h	4.74 ± 1.15 h
Ascending colon: disappearance	13.57 ± 4.45 h	10.88 ± 1.48 h
Overall transit time in colon	19.92 ± 1.39 h	17.37 ± 4.80 h

Plasma C_{max} values of 5-ASA and Ac-5-ASA during steady-state were about 1.4 and 1.2 fold higher after once daily dosing (o.d.) when compared to values obtained after dosing three times daily (t.i.d.) dosing of the same daily dose. Plasma trough levels at the end of the dosing interval were only slightly (0.3 and 0.4 times, 5-ASA and Ac-5-ASA respectively) lower after o.d. dosing when compared to that after t.i.d. dosing. There is no indication of systemic drug accumulation, when given o.d.

The administration of a single oral dose of SALOFALK granules, 20 mg/kg body weight, in 13 children with active colonic inflammatory bowel disease (IBD) (age range: 5.9 to 15.8 years) showed that the pharmacokinetics of systemic exposure in children corresponds with those in adults. SALOFALK was safe and well tolerated.

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, ESR, and haemoglobin. These criteria have been summarised in the clinical activity index (CAI) to evaluate the efficacy of treatment for ulcerative colitis.

The safety and efficacy of SALOFALK granules (1.5 g to 3 g 5-ASA/day) was compared against mesalazine tablets (SALOFALK 500 mg tablets, 1.5 g to 3.0 g 5-ASA/day) in a double-blind randomised multi-centre study in 233 patients with mild to moderately active ulcerative colitis over a period of 8 weeks. The primary efficacy criterion, complete response rate (per protocol analysis, PP) was very similar in the granules (68%) and the tablets (70%) groups. The efficacy analysis (PP) showed that more patients treated with mesalazine tablets (47%) had to increase the dose from 1.5 g mesalazine/day to 3.0 g mesalazine/day compared to patients treated with granules (38%). Similar results were obtained by the ITT (intention-to-treat) analysis: 39% of the granules group, 45% of the tablets group, i.e., more patients came into remission (49%) with the 1.5 g 5-ASA/day from granules than from tablets (43%). Granules, therefore, in total were as efficacious and as well tolerated as the tablets at the same dose. Subgroup analyses showed that the response rates to granules were higher in patients with high baseline disease activity (CAI>8) and with 1 or more extraintestinal manifestations than the tablets:

Parameters	Granules	Tablets
CAI ≤8	67%	74%
CAI >8	65%	44%
Extraintestinal Manifestation:		
-none	69%	72%
-1 or more	53%	36%

In another study, the efficacy and safety of SALOFALK granules of different dosages (1.5 g, 3.0 g, 4.5 g/day) were compared in 321 patients with mild to moderately active ulcerative colitis in a double-blind manner for a treatment period of 8 weeks. Complete response (CAI ≤ 4) was obtained by 50% in the 1.5 g dose group, by 66% in the 3.0 g group (in comparison to 1.5 g: p = 0.014) and by 55% in the 4.5 g group (in comparison to 1.5 g: not significant, p=0.318). The 3.0 g/day dose appears to be the optimal dose.

In a double-blind, randomised comparative study, the efficacy and tolerability of once daily (o.d.) 3.0 g SALOFALK granules was compared with three time daily (t.i.d.) 1.0 g SALOFALK granules in 380 patients with active ulcerative colitis over a period of eight weeks. The data show that for SALOFALK granules, a daily dose of 3 g mesalazine given o.d. is therapeutically equivalent to the conventional t.i.d. dosage regimen for the induction of remission (CAI ≤ 4) in patients with mild-to-moderate ulcerative colitis. The clinical remission rate in the PP analysis set (primary analysis) was 84.4% in the o.d. group and 81.3% in the t.i.d. group. The resulting p-value for

the non-inferiority test (pre-defined margin: -15%) was 0.0007 with a 95% CI of [-11.4%, 17.6%]. With the achieved lower boundary of the derived 95% CI of 3.1%, an even narrower margin for the non-inferiority was kept. Remission rates in ITT analysis set were very similar, 80.8% in the o.d. group and 77.4% in the t.i.d. group. ITT test result (p = 0.0007) and 95% CI (-11.4%, 18.1%) agreed with the PP analysis. Once daily dosing of SALOFALK granules was as safe and well tolerated as three times daily dosing of SALOFALK granules.

Results of the various studies show that oral delayed release SALOFALK granules are well tolerated in patients with ulcerative colitis.

INDICATIONS

SALOFALK granules are indicated in the treatment of acute ulcerative colitis of mild to moderate severity, and for the maintenance of remission and/or the long term treatment of ulcerative colitis.

CONTRAINDICATIONS

SALOFALK granules and tablets are contraindicated in patients with the following:

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

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, 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.

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.

In the case of phenylketonuria, it should be borne in mind that SALOFALK granules contain aspartame as a sweetening agent, equivalent to the following quantities of phenylalanine:

SALOFALK granules equivalent to:	Aspartame equivalent to the following Quantity of phenylalanine:
500 mg mesalazine	0.56 mg
1 g mesalazine	1.12 mg
1.5 g mesalazine	1.68 mg
3 g mesalazine	3.36 mg

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 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 representing about the same, and 3.5 times, the maximal recommended clinical dose of Salofalk granules 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 a neonate was reported. Salofalk granules 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 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. There is no experience with

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

Paediatric use

SALOFALK should not be used in children below 6 years of age, as there is very limited 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 4g/60 mL 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
• Lactulose or similar preparations, which lower stool pH:	possible reduction of mesalazine release from granules due to decreased pH caused by bacterial metabolism

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 frequent adverse reactions seen in clinical trials are headache (3%), abdominal pain (4%), exacerbation of ulcerative colitis (2%), abnormal hepatic function (2%) and upper respiratory tract infection (1%).

In two clinical trials involving 550 patients with acute ulcerative colitis, tolerability was good. The table below shows the adverse events that occurred in at least 5% of patients in the clinical trials:

Adverse event	**SAG-2/UCA**			**SAG-15/UCA**	
	Salofalk 0.5 g tds (n = 102)	**Salofalk 1 g tds (n = 108)**	**Salofalk 1.5 g tds (n = 108)**	**Salofalk 0.5 – 1 g tds granules (n = 114)**	**Salofalk 0.5 – 1 g tds tablets (n=118)**
	AE/ Potential ADR	AE/ Potential ADR	AE/ Potential ADR	AE/ Potential ADR	AE/ Potential ADR
Headache	24%/3%	23%/12%	21%/4%	6%/3%	7%/3%
Abdominal pain	5%/1%	7%/4%	7%/4%	-	-
Ulcerative colitis aggravated	15%/2%	6%/1%	7%/0	5%/1%	8%/1%
Hepatic function abnormal	1%/1%	3%/2%	5%/5%	-	-
Upper resp tract infection	3%/0	4%/1%	7%/1%	-	-
Influenza like symptoms	-	-	-	3%/0	6%/0

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

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

For adults and the elderly:
Unless otherwise prescribed, the recommended dose for acute ulcerative colitis is 1.5 g to 3 g per day. For maintenance of remission and/or long term treatment of ulcerative colitis, the recommended dose is 1.5 g per day.

For children older than 6 years of age:
The recommended dose for acute ulcerative colitis, depending on disease severity, is 30-50 mg mesalazine/kg/day. For maintenance of remission and/or long term treatment of ulcerative colitis, the recommended dose is 15-30 mg mesalazine/kg/day.

Doses may be given in one to three divided doses.

It is generally recommended that half the adult dose may be given to patients up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

SALOFALK should not be used in children below 6 years of age, as there is very limited experience with this age group.

SALOFALK granules should be swallowed without chewing with sufficient fluid. If granules are taken together with meals the gastric passage might be delayed for 1-2 hours, but does not influence the release profile and plasma concentrations.

SALOFALK should be used on a regular basis and consistently, in the treatment of acute inflammatory episode, in order to achieve the desired therapeutic effect. In general, an acute episode of ulcerative colitis usually subsides by 8 weeks.

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 granules are presented as greyish white cylindrical or round particles.

They are available in aluminium sachets of 500 mg, 1 g or 1.5 g doses of mesalazine.

500 mg sachets are available in packs of 50*, 100, or 300* sachets.
1 g sachets are available in packs of 50*, 100, or 150* sachets.
1.5 g sachets are available in packs of 60 or 100* sachets.
(*currently not available)

STORAGE CONDITIONS

Store below 25˚C.

NAME AND ADDRESS OF THE SPONSOR

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

Website: www.orphan.com.au

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

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

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