# AUSTRALIAN PRODUCT INFORMATION

# SALOFALK® (mesalazine) enteric coated tablets

## 1. NAME OF THE MEDICINE

SALOFALK mesalazine enteric coated tablets
Mesalazine.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALOFALK tablets contain either 500 mg or 1 g mesalazine, as the active ingredient.

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

Excipients with known effect in SALOFALK 500 mg tablets: each table contains 49 mg of elemental sodium.

See section 4.4 Special warnings and precautions for use.

## 3. PHARMACEUTICAL FORM

Salofalk tablets have a functional coating, 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.

SALOFALK 500 mg enteric coated tablets are presented as butter-yellow to ochre, oblong tablets.

SALOFALK 1 g enteric coated tablets are presented as yellow to ochre, oblong tablets.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

SALOFALK tablets are indicated in the treatment of acute episodes and maintenance of remission of:
i. Mild to moderate ulcerative colitis; and
ii. Crohn's ileitis and colitis

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Unless otherwise prescribed, the recommended doses given in one to three divided doses **for adults and the elderly** are as follows -:

For acute treatment of:

| | |
|---|---|
| Ulcerative colitis - | 1.5 g to 3 g per day |
| Crohn's ileitis and colitis - | 3 g to 4.5 g per day |

For maintenance of remission and/or long-term treatment of:

| | |
|---|---|
| Ulcerative colitis - | 1.5 g per day |
| Crohn's ileitis and colitis - | 1.5 g to 3 g per day |

Depending on disease severity in **children older than 6 years of age**, the recommended doses, given in one to three divided doses, for the treatment of ulcerative colitis are as follows:

For acute treatment: 30-50 mg mesalazine/kg (body weight)/day.

For maintenance of remission and/or long-term treatment: 15-30 mg mesalazine/kg (body weight)/ day.

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. The total daily dose should not exceed the maximum adult dose.

SALOFALK tablets should not be used in children below 6 years of age for the treatment of acute episodes and maintenance of remission of mild to moderate ulcerative colitis, as there is very limited experience with this age group.

SALOFALK tablets should not be used in children below 12 years of age for the treatment of Crohn's ileitis and colitis, as there is very limited experience with this age group.

SALOFALK tablets should be swallowed without chewing or crushing with sufficient fluid. The tablets should be taken at least 1 hour before a meal in order to allow for gastric emptying.

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 or Crohn's ileitis and colitis usually subsides by 8 weeks.

In rare cases of patients who have undergone intestinal resection or bowel surgery of the ileocaecal region with removal of the ileocaecal valve, undissolved SALOFALK tablets have been eliminated in stools due to an excessively rapid intestinal passage.

## 4.3 CONTRAINDICATIONS

SALOFALK tablets are contraindicated in patients with the following:

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

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SALOFALK should be taken 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 tablets 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, γGT) 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 tablets 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 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 tablets should then be discontinued immediately if 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 tablets 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. SALOFALK tablets 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.

**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 tablets should not be used in children below 6 years of age for the treatment of acute episodes and maintenance of remission of mild to moderate ulcerative colitis, as there is very limited experience with this age group.

SALOFALK tablets should not be used in children below 12 years of age for the treatment of Crohn's ileitis and colitis, as there is very limited experience with this age group.

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

**Excipients with known effect**
Salofalk 500mg tablets contain 49 mg sodium per tablet. The maximum daily dose of sodium is 441 mg per day. This should be particularly taken into account for those on a low salt diet.

## 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 |
| • Lactulose or similar preparations, which lower stool pH: | possible reduction of mesalazine release from tablets due to decreased pH caused by bacterial metabolism |

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 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 3$^{rd}$ and 5$^{th}$ months of pregnancy, renal failure in a neonate was reported.

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

The most frequent adverse reactions seen in clinical trials of SALOFALK tablets 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 mild to moderate 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 500 mg tds (n =** | **SALOFALK 1 g tds (n = 108)** | **SALOFALK 1.5 g tds (n = 108)** | **SALOFALK 500 mg – 1 g tds** | **SALOFALK 500 mg – 1 g tds** |
| | 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 all SALOFALK preparations including SALOFALK tablets. In many cases, the relationship to SALOFALK treatment 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, dyspepsia 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, 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

***Skin and Appendages Disorders***
Alopecia, allergic exanthema, increased sweating

***Urinary System Disorders***
Acute or chronic interstitial nephritis, renal insufficiency, renal failure, nephrotoxicity

***White Cell and RES Disorders***
Agranulocytosis, leukopenia, neutropenia, pancytopenia

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

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

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

***Liver and Biliary System Disorders***
Cholestatic hepatitis

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

***Urinary System Disorders***
Nephrolithiasis (see section 4.4 Special Warnings and Precautions for Use for further information).

***Skin and subcutaneous tissue disorders SOC***
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).

## 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, 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 on 131126 (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**
*Ulcerative colitis*
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 mesalazine/day) was compared against mesalazine tablets (SALOFALK 500 mg tablets, 1.5 g to 3.0 g mesalazine/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 mesalazine/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:

| Baseline Parameters | SALOFALK Granules Group | SALOFALK Tablets Group |
|---|---|---|
| CAI ≤8 | 67% | 7 |
| CAI >8 | 65% | 4 |
| Extraintestinal Manifestation: | | |
| -none | 69% | 7 |
| -1 or more | 53% | 3 |

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 $\leq 4$) 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 $\leq$ 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 the 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.

*Crohn's ileitis and colitis*
The clinical pattern of symptoms and complications of Crohn's disease is more varied than that of ulcerative colitis. The criteria used to evaluate the efficacy of the substance in the therapy of Crohn's disease are summarised in the Crohn's disease Activity Index (CDAI) and consist of stool frequency, abdominal pain rating, well-being scale ratings, use of loperamide or codeine to control diarrhoea, body weight, haematocrit, presence of abdominal masses and physicians' assessment of patients' wellbeing.

Four controlled studies ranging in duration from 8 to 12 weeks have been performed to investigate the efficacy of Salofalk in comparison to standard therapies such as glucocorticosteroids and the combination glucocorticosteroids/sulfasalazine in the treatment of Crohn's disease. In a randomised controlled trial of 3 month duration, there was no difference in efficacy between the group taking 3 g/d Salofalk (3 x 2 Salofalk 500 mg tablets), in comparison with the group taking a combination of sulphasalazine (3 g) and methylprednisolone (initial 40 mg, then weekly reduction by 4 mg). Clinical remission could be observed in 83% of the mesalazine group in comparison to 88% of the sulphasalazine group. There was no statistically significant difference between the groups.

In another randomised controlled multicentre trial of 3 month duration, following the administration of 3g mesalazine (3 x 4 tablets Salofalk 250 mg) or prednisone (initially 40 mg, then weekly reduction by 4 mg) to Crohn's disease patients, the reduction and maintenance of reduction in CDAI scores were similar in the two groups. There was no statistically significant ($p \geq 0.05$) difference between treatments in the reduction in CDAI score at week 12. In a further study, high-dose Salofalk (3x3 Salofalk 500 mg = 4.5g) was compared with 6-methylprednisolone (initially 48 mg, weekly tapering for 8 weeks to 8 mg per day) in the therapy of Crohn's disease. Following 8 weeks of therapy, 40% of the patients in the mesalazine group and 56.3% of the patients in the 6-methylprednisolone group were in remission (CDAI<150 and a decrease of at least 60 points, p=0.5867). The fourth trial (n=40) comparing the efficacy and safety of mesalazine 1.5 g/day with sulphasalazine 3 g/day provides supportive evidence that Salofalk is as effective as standard therapy. The fall in CDAI from baseline to 8 weeks was statistically significant for both treatments, while the mean reduction in CDAI score was greater with mesalazine than with sulphasalazine (196.477 vs 139.0).

Four placebo-controlled studies investigated the efficacy of mesalazine in the maintenance of remission of Crohn's disease. The dosages varied from 1 to 3 g/day mesalazine with a follow up period ranging from 1 to 1.5 years. The patients in the trials had either medically or surgically induced remission. All trials showed a significant improvement in the use of mesalazine when compared to placebo. In one of these trials involving 59 Crohn's patients on a treatment dosage of 1g/d mesalazine and one year follow up, the recurrence rate in the mesalazine group was 27% compared with 55% in the placebo group ($p<0.05$). In another multi-centre study involving 163 patients receiving prophylactic treatment with 3 g mesalazine/day for up to 72 months, the symptomatic recurrence rate in the mesalazine

group was significantly reduced in comparison with the placebo group (31% vs. 41%, p=0.031). In the third placebo controlled study, including 206 patients, treated with 1.5 g/day mesalazine for up to 12 months, the relapse estimate was significantly lower in patients with ileal disease (8.3% on mesalazine vs. 31% on placebo, p=0.0535) and in patients with previous bowel resection (14.2% vs. 47%, p=0.0435). The fourth study, including 66 patients, showed that patients with Crohn's ileocolitis appeared to respond best to mesalazine (p=0.09).

Results of the various studies show that oral delayed release SALOFALK tablets are well tolerated in patients with ulcerative colitis and Crohn's ileitis and colitis.

## 5.2 PHARMACOKINETIC PROPERTIES

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 no pharmacokinetic data in the elderly using SALOFALK tablets.

**Absorption:**
The systemic absorption of mesalazine decreases in the intestinal tract from proximal to distal segments. Because of low systemicabsorption rates from oral delayed release preparations or rectal applications forms of mesalazine, 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, 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. Less than 1% mesalazine and about 24% N-acetyl-5-ASA based on the administered mesalazine dose are excreted in the urine. Biliary excretion is a minor route of elimination.

**SALOFALK tablets:**
SALOFALK tablets are gastric juice resistant and release mesalazine in the terminal ileal region in a pH dependent manner due to the Eudragit-L coating. Under starved condition the tablet transit time from the stomach to the small intestine is (0.79 ± 0.7 hours). It is recommended that tablets are taken about 1 hour before a meal to avoid dose-dumping.

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):

| | SALOFALK Granules | | SALOFALK 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 respectively. 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% of administered mesalazine dose from both SALOFALK formulations 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 mesalazine 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, mesalazine 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.

## 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 4 g/60 mL enema.

## 6. PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

SALOFALK 500mg tablets contain sodium carbonate, glycine, povidone, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, calcium stearate, hypromellose, methacrylic acid copolymer, purified talc, titanium dioxide, iron oxide yellow, macrogol 6000, Eudragit E100.
SALOFALK 1g tablets contain povidone, microcrystalline cellulose, croscarmellose sodium, methacrylic acid copolymer, calcium stearate, purified talc, macrogol 6000, hypromellose, colloidal anhydrous silica, iron oxide yellow and titanium dioxide.

## 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. Store in a dry place and protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

SALOFALK 500 mg tablets: PVC/PE/PVdC/Aluminium orange blister strips packed in cardboard. Pack sizes of 10 and 100 tablets.

SALOFALK 1 g tablets: PVC/PVdC/Aluminium orange blister strips packed in cardboard. Pack sizes of 10 (starter pack), 20, 50, 60, 90, 100 and 150 tablets.

Not all pack sizes are currently available in Australia.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

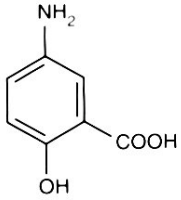
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Mesalazine is a white to greyish, voluminous powder, slightly pink in colour. It is practically insoluble in ethanol (90%), methanol (70%), water, ether, and chloroform, soluble in HCl (warmed 10% solution); soluble in NaOH (10% solution, with salt formation).

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

**Chemical structure**




**CAS number**
89-57-6

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8. SPONSOR

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

Phone: 1800 DRFALK (373 255)

## 9. DATE OF FIRST APPROVAL

SALOFALK 500 mg: 28 February 2007

SALOFALK 1 g: 16 January 2018

## 10. DATE OF REVISION

8 September 2023

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

**Summary table of changes**

| Section/s changed | Summary of new information |
|---|---|
| 1, 3, 4.2, 4.3, 4.4, 4.6, 4.7. 4.8, 5.1, 5.2, 5.3 | Minor editorial changes |
| 4.2, 4.4, 4.6, 4.8 | 4.2 statement added to not exceed maximum dose<br>4.4 update to sections relating to blood dyscrasia and epigastric pain, addition of DRESS and statement on urine discolouration<br>4.6 update to Use in lactation section<br>4.8 addition of dyspepsia, changes in pancreatic enzymes, eosinophil count increased and DRESS. |