PROFESSIONAL INFORMATION FOR

SALOFALK 500 mg/1000 mg/1,5 g (gastro-resistant prolonged-release granules)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SALOFALK 500 mg gastro-resistant prolonged-release granules

SALOFALK 1 000 mg gastro-resistant prolonged-release granules

SALOFALK 1,5 g gastro-resistant prolonged-release granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALOFALK 500 mg:

Each sachet of SALOFALK 500 mg contains 500 mg mesalazine.

Contains sugar: sucrose 0,02 mg.

Contains sweetener: aspartame 1,0 mg.

SALOFALK 1 000 mg:

Each sachet of SALOFALK 1 000 mg contains 1 000 mg mesalazine.

Contains sugar: sucrose 0,04 mg.

Contains sweetener: aspartame 2,0 mg.

SALOFALK 1,5 g:

Each sachet of SALOFALK 1,5 g contains 1,5 g mesalazine.

Contains sugar: sucrose 0,06 mg.

Contains sweetener: aspartame 3,0 mg.

For the full list of excipients, **see section 6.1**

3. PHARMACEUTICAL FORM

Gastro-resistant prolonged-release granules

The granules are rounded, stick-formed or round particles, greyish white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SALOFALK is indicated for the treatment of acute episodes and the maintenance of remission of ulcerative colitis.

4.2 Posology and method of administration

Posology

Adults and the elderly

For the treatment of acute episodes of ulcerative colitis

Once daily, 1 – 2 sachets of SALOFALK 1,5 g, 3 sachets of SALOFALK 1 000 mg or 3 sachets of SALOFALK 500 mg (equivalent to 1,5 – 3,0 g mesalazine daily) preferably to be taken in the morning according to the individual clinical requirement.

It is also possible to take the prescribed daily dose in three divided doses (1 sachet of SALOFALK 500 mg 3 times daily or 1 sachet of SALOFALK 1 000 mg 3 times daily) if this is more convenient for the patient.

For the maintenance of remission of ulcerative colitis

The standard treatment is 0,5 g mesalazine 3 times daily (in the morning, at midday and in the

evening) corresponding to a total dose of 1,5 g mesalazine per day.

For patients known to be at increased risk for relapses for medical reasons or due to difficulties to adhere to application of three daily doses, the dosing schedule can be adapted to 3,0 g mesalazine given as a single daily dose, preferably in the morning.

Paediatric population

There is only limited documentation for an effect in children (age 6 – 18 years).

Children 6 years of age and older

Active disease: To be determined individually, starting with 30 – 50 mg/kg bw/day once daily preferably in the morning or in divided doses. Maximum dose: 75 mg/kg bw/day. The total dose should not exceed the maximum adult dose.

Maintenance treatment: To be determined individually, starting with 15 – 30 mg/kg bw/day in divided doses. The total dose should not exceed the recommended adult dose.

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

Method of administration

The contents of the sachets of SALOFALK granules should not be chewed. The granules should be taken on the tongue and swallowed, without chewing, with plenty of liquid.

Both in the treatment of acute inflammatory episodes and during long term treatment, SALOFALK granules should be used on a regular basis and consistently in order to achieve the desired therapeutic effects.

The duration of use is determined by the medical practitioner.

4.3 Contraindications

- Hypersensitivity to mesalazine, to salicylates or to any of the excipients of SALOFALK (see **section 6.1**)
- Severe impairment of hepatic or renal function.
- ≥ 20 weeks Pregnancy (see **section 4.6**)

4.4 Special warnings and precautions for use

- Blood tests (differential blood count; liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating medical practitioner. As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks.

  If the findings are normal, follow-up tests should be carried out every three months.

  If additional symptoms occur, these tests should be performed immediately.

- Caution is recommended in patients with impaired hepatic function.
- SALOFALK granules should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.
- Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100 % mesalazine content. It is recommended to ensure adequate fluid intake during treatment.
- Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with SALOFALK granules.
- Patients with a history of adverse drug reactions to preparations containing sulfasalazine should be kept under close medical surveillance on commencement of a course of treatment with SALOFALK granules. Should SALOFALK granules cause acute intolerance

reactions, such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

- This medicine contains 1,0 mg/ 2,0 mg/ 3,0 mg aspartame in each sachet of SALOFALK 500 mg/1 000 mg/ 1,5 g. Aspartame is a source of phenylalanine. It may be harmful in patients with phenylketonuria (PKU).
- SALOFALK granules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially ‘sodium-free’.
- Use of NSAIDs, such as SALOFALK granules, around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion dialysis, in some cases.
- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as SALOFALK granules. Some of these events have been fatal or life-threatening.

  DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

If such signs or symptoms are present, discontinue SALOFALK granules and evaluate the patient immediately.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed.

- Lactulose or similar preparations lower stool pH: possible reduction of mesalazine which release from granules due to decreased pH caused by bacterial metabolism of lactulose.
- In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine should be taken into account.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of SALOFALK granules in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the foetus/newborn child. To date no other relevant epidemiologic data are available. In one single case after long-term use of high dose mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Breastfeeding

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in women is available to date. Hypersensitivity reactions, like diarrhoea in the infant, cannot be excluded. If the infant develops diarrhoea, the breastfeeding should be discontinued.

Regular use of non-steroidal inflammatory drugs may result in:

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Second and Third trimester

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

4.7 Effects on ability to drive and use machines

SALOFALK granules have no influence or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent:	Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia).

Nervous system disorders:

Frequent:	Headache
Less frequent:	Dizziness, Peripheral neuropathy.

Cardiac disorders:

Less frequent:	Myocarditis, pericarditis

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)

Gastrointestinal disorders:

Frequent:	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, acute pancreatitis

Renal and urinary disorders:

Less frequent:	Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency
Frequency unknown:	Nephrolithiasis *

Skin and subcutaneous tissue disorders:

Less frequent:	Photosensitivity, alopecia

Musculoskeletal and connective tissue disorders:

Less frequent:	Arthralgia, myalgia

Immune system disorders:

Less frequent:	Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis

Hepatobiliary disorders:

Less frequent:	Changes in liver function parameters (increase in transaminases and parameters of cholestasis), cholestatic hepatitis, hepatitis

Reproductive system and breast disorders:

Less frequent:	Oligospermia (reversible)

General disorders:

Less frequent:	Asthenia, fatigue

Investigations:

Frequent:	Changes in liver function parameters (increase in transaminases and parameters of cholestasis), changes in pancreatic enzymes (lipase and amylase increased), eosinophil count increased.

* see section 4.4 for further information

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) [see **section 4.4**]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla at drugsafetysa@cipla.com

4.9 Overdose

Preclinical data suggest that renal toxicity could be expected upon intoxication with mesalazine. There is no specific antidote and treatment is symptomatic and

supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 11.10 Medicines acting on the gastro-intestinal tract – Other.

Pharmacotherapeutic group: Intestinal anti-inflammatory agents; Aminosalicylic acid and similar agents

ATC code: A07EC02

Mechanism of action

The mechanism of the anti-inflammatory action is unknown. The results of in vitro studies indicate that inhibition of lipoxygenase may play a role.

Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated. Mesalazine (5-aminosalicylic acid / 5-ASA) may also function as a radical scavenger of reactive oxygen compounds.

Pharmacodynamic effects

Mesalazine, orally administered, acts predominantly locally at the gut mucosa and in the submucosal tissue from the luminal side of the intestine. It is important, therefore, that mesalazine is available at the regions of inflammation. Systemic bioavailability/plasma concentrations of mesalazine are therefore of no relevance for therapeutic efficacy, but rather a factor for safety. In order to realise this, SALOFALK granules are gastric juice resistant and release mesalazine in a pH dependent manner, due to an Eudragit L coating, and prolonged manner, due to the matrix granule structure.

5.2 Pharmacokinetic properties

Pharmacokinetic properties:

General considerations of mesalazine

Absorption

Mesalazine absorption is highest in proximal and lowest in distal gut areas.

Biotransformation

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43 % and 78 %, respectively.

Elimination

Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the faeces (major part), renally (varies between 20 and 50 %, depending on the kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-Ac-5-ASA. About 1 % of the total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

SALOFALK Granules specific

Distribution

Owing to the granule size of approximately 1 mm, transit from the stomach to the small intestine is fast.

A combined pharmacoscintigraphic/pharmacokinetic study showed that the compound reaches the ileocaecal region within approx. 3 hours and the ascending colon within approx. 4

hours. The total transit time in the colon amounts to about 20 hours.

Approximately 80 % of an administered oral dose is estimated to be available in the colon, sigmoid colon and rectum.

Absorption

Mesalazine release from SALOFALK granules starts after a lag phase of about 2 – 3 hours. Peak plasma concentrations are reached at about 4 – 5 hours. The systemic bioavailability of mesalazine after oral administration is estimated to be approximately 15 – 25 %.

Food intake delays absorption by 1 to 2 hours but does not change the rate and extent of absorption.

Elimination

From a 3 x 500 mg daily mesalazine dose in long-term therapy, a total renal elimination of mesalazine and N-Ac-5-ASA under steady state conditions was calculated to be about 25 %. The unmetabolised excreted mesalazine part was less than 1 % of the oral dose. The elimination half-life in this study was 4,4 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction. Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Aspartame
- Cellulose, microcrystalline
- Citric acid, anhydrous
- Hypromellose
- Magnesium stearate
- Methacrylic acid-methyl methacrylate copolymer (1:1) [Eudragit L 100]
- Methylcellulose
- Polyacrylate Dispersion 40 % (contains 2 % Nonoxynol as emulsifier) [= Eudragit NE 40D]
- Povidone
- Silica, colloidal anhydrous
- Simethicone
- Sodium carboxymethylcellulose
- Sorbic acid
- Talc
- Titanium dioxide
- Triethyl citrate
- Vanilla custard flavouring (containing sucrose)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 30 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

SALOFALK granules are packed into sachets consisting of a PET12/ ALU9/ PE50 foil in which the PE-layer is in direct contact with the medicine.

SALOFALK 1,5 g : 35, 70 or 100 sachets are packed in a printed cardboard carton.

SALOFALK 500 mg: 50 , 100 or 300 sachets are packed in a printed cardboard carton.

SALOFALK 1 000 mg: 50 , 100 or 150 sachets are packed in a printed cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530,

RSA

Company Contact Details

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

SALOFALK 1,5 g: 43/11.10/0086

SALOFALK 500 mg: 43/11.10/0195

SALOFALK 1 000 mg: 43/11.10/0196

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 24 May 2022

Date of latest renewal: Not applicable

10. DATE OF RIVISION OF THE TEXT

Not applicable