

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrSALOFALK®

Mesalamine Suppositories

Suppositories, 500 mg and 1000 mg, Rectal

Lower Gastrointestinal Tract Anti-Inflammatory

(ATC A07EC02)

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Renal	06/2023
7 WARNINGS AND PRECAUTIONS, Skin	06/2023
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast Feeding	11/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SALOFALK® (mesalamine suppositories) is indicated for:

- management of ulcerative proctitis.
- as adjunctive therapy in more extensive distal ulcerative colitis (DUC).

1.1 Pediatrics

Information on the safety and efficacy of SALOFALK in children is limited. Therefore, use should be limited to situations where a clear benefit is expected. SALOFALK should not be used in infants under two years of age.

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

SALOFALK is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- patients with severe renal impairment (GFR<30ml/min/1.73m²) and/or severe hepatic impairment. See 7 WARNINGS AND PRECAUTIONS.
- cases of existing gastric or duodenal ulcer.
- patients with urinary tract obstructions.
- patients hypersensitive to salicylates, including acetylsalicylic acid (e.g. Aspirin®), may also be hypersensitive to this medication.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- One 500 mg SALOFALK rectal suppository is self-administered on a twice a day or three times a day basis. One 1000 mg SALOFALK rectal suppository is self-administered on a once daily basis, at bedtime. The usual adult dose is 1.0 - 1.5 g/day and dosing is continued until a significant response is achieved or until the patient achieves remission. Dose tapering is recommended. Abrupt discontinuation is not recommended. Best results are expected with prolonged retention.

Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics.

4.4 Administration

For rectal use only. SALOFALK suppositories are self-administered, one 500 mg suppository 2 or 3 times/day, and one 1000 mg suppository 1 time daily at bedtime. The suppository should be retained

for 1 to 3 hours or longer to achieve the maximum benefit. While the effect of the suppositories may be seen within 3 to 21 days, the usual course of therapy would be from 3 to 6 weeks depending on symptoms and sigmoidoscopic findings.

Patient Instructions:

- I. Detach one suppository from the strip of suppositories.
- II. Hold suppository upright and carefully remove the plastic wrapper.
- III. Avoid excessive handling of suppository, which is designed to melt at body temperature.
- IV. Insert suppository completely into rectum with gentle pressure, pointed end first.
- V. A small amount of lubricating gel may be used on the tip of the suppository to assist insertion.

In children, information on the safety and efficacy of mesalamine suppositories is limited. Therefore, use should be limited to situations where a clear benefit is expected.

4.5 Missed Dose

If a dose of SALOFALK is missed, it should be used as soon as possible, unless it is almost time for the next dose. A patient should not use two doses at the same time to make up for a missed dose.

5 OVERDOSAGE

There has been no clinical experience with mesalamine overdose. However, because mesalamine is an aminosalicilate, the symptoms of overdose may mimic the symptoms of salicylate overdose; therefore, measures used to treat salicylate overdose may be applied to mesalamine overdose. Under ordinary circumstances, local mesalamine absorption from the colon is limited. There is no specific antidote and treatment is symptomatic and supportive.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Rectal	suppositories 500mg, 1000 mg	Witepsol H-15 (suppository wax base).

SALOFALK is gluten-free and phthalate-free.

Each smooth light tan to grey, bullet-shaped suppository is available in strips of 6, boxes of 30 suppositories.

7 WARNINGS AND PRECAUTIONS

General

SALOFALK should be used only if the benefits clearly outweigh the risks in patients with underlying, bleeding or clotting disorders as well as during pregnancy and lactation.

Patients with renal dysfunction, or elevated Blood Urea Nitrogen (BUN), or elevated serum creatinine, or with proteinuria, should be carefully monitored while receiving SALOFALK.

Concomitant treatment with mesalamine can increase the risk of myelosuppression in patients receiving azathioprine or 6-mercaptopurine.

Acute Intolerance Syndrome

Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be re-evaluated. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. The possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on concurrent mesalamine products which contain or release mesalamine and those with pre-existing renal disease should be carefully monitored with urinalysis, and BUN and creatinine testing.

Carcinogenesis and Mutagenesis

Carcinogenicity studies in animals and mutagenicity tests were negative. See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Cardiac side effects, including pericarditis and myocarditis have been uncommonly reported with the use of mesalamine.

Cases of pericarditis have also been reported as manifestations of inflammatory bowel disease. Discontinuation of mesalamine may be warranted in some cases, but rechallenge with mesalamine can be performed under careful clinical observation should the continued therapeutic need for mesalamine be present.

Driving and Operating Machinery

There are no data available on the effects of mesalamine on ability to drive and use machines.

Gastrointestinal

Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or sulfasalazine (SAS) therapy (18%), should be investigated in order to exclude pericarditis and pancreatitis either as adverse drug reactions to mesalamine or secondary manifestations of inflammatory bowel disease.

Hepatic/Biliary/Pancreatic

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with 5-Amino salicylic acid (5-ASA)/Mesalazine products. Therefore, SALOFALK is contraindicated in patients with severe hepatic impairment. See 2 CONTRAINDICATIONS. In patients with mild to moderate liver function impairment, caution should be exercised and SALOFALK should only be used if the expected benefit clearly outweighs the risks to the patients.

Renal

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine products and pro-drugs of mesalamine. SALOFALK is contraindicated in patients with severe renal impairment. See [2 CONTRAINDICATIONS](#). In patients with mild to moderate renal dysfunction history of renal disease or using concomitant nephrotoxic drugs, caution should be exercised and SALOFALK should be used only if the benefits outweigh the risks.

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 on mesalamine, especially those with pre-existing renal disease, should be carefully monitored with urinalysis, and BUN and creatinine testing. Initial assessment and periodic monitoring of the renal function is recommended since mesalamine is substantially excreted by the kidney, and prolonged mesalamine therapy may damage the kidneys. Discontinue SALOFALK if renal function deteriorates while on therapy.

Because elderly patients are more likely to have decreased renal function, closer monitoring of the renal function may be needed.

Sensitivity/Resistance

Caution should be exercised when mesalamine (5-ASA) is initially used in patients known to be allergic to sulfasalazine. These patients should be instructed to discontinue therapy if sign of rash or pyrexia become apparent. In case of an allergic reaction, appropriate measures (standard of care) should be taken.

Skin

Severe Cutaneous Reactions:

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalamine treatment. Mesalamine should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Photosensitivity:

Patients treated with mesalamine or sulfasalazine who have pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

7.1 Special Populations

7.1.1 Pregnant Women

SALOFALK should be used during pregnancy only if the benefits clearly outweigh the risks to the foetus. 5-ASA is known to cross the placental barrier, and no clinical studies have been performed in pregnant women.

Animal studies did not show evidence of impaired fertility or harm to the foetus due to mesalamine see [16 NON-CLINICAL TOXICOLOGY](#), however, because animal reproduction studies are not always predictive of human response, SALOFALK should be used during pregnancy only if clearly needed.

7.1.2 Breast-feeding

There are no clinical trial studies in nursing women. SALOFALK should be used in nursing women only if the benefits to the mother clearly outweigh the risks to the child. Mesalamine and its main metabolite N-acetyl-5-ASA are excreted in breast milk. The concentration of mesalamine is much lower than in maternal blood, but the metabolite N-acetyl-5-ASA appears in similar concentrations.

When mesalamine is used in nursing women, infants should be monitored for changes in stool consistency. If the infant develops diarrhoea breast-feeding should be discontinued. Cases of diarrhoea in breastfed infants exposed to mesalamine have been reported.

Isolated weight decrease in nursing infant has been reported during post-marketing experience with mesalamine.

7.1.3 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Clinical studies of mesalamine did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Mesalamine is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Hypersensitivity reactions have been reported in a sub-group of patients known to be allergic to sulfasalazine including rash, pyrexia, and dizziness with reactions occurring at the onset of therapy and resolving promptly following discontinuation.

Other manifestations of hypersensitivity reported with mesalamine include acute pancreatitis, hepatitis, pericarditis, interstitial nephritis, interstitial pneumonia and pleural effusion. Interstitial pneumonia, pancreatitis and pericarditis have also been reported as manifestations of inflammatory bowel disease.

As with all 5-ASA products, exacerbations of ulcerative colitis characterized by cramping acute abdominal pain and diarrhoea have been reported with mesalamine.

Other reported side effects include headache, flatulence, nausea, and hair loss, but do not appear to be common. Retreatment is not always associated with repeated hair loss. Aplastic anaemia has been reported in the literature with unspecified formulations of mesalamine.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 Clinical Trial Adverse Events Reported in > 0.1% of Patients

	SALOFALK N=841 %	Placebo N=176 %
Cardiac Disorders		
Pericarditis	0.1	0.0
Gastrointestinal Disorders		
Abdominal pain	7.9	7.9
Flatulence	6.0	4.5
Nausea	5.6	6.8
Diarrhoea	2.1	3.9
Abdominal distension	1.4	1.1
Haemorrhoids	1.3	0.0
Proctalgia	1.1	0.0
Constipation	0.9	2.2
Anorectal discomfort	0.5	1.7
Pancreatitis	0.1	0.0
Condition aggravated	0.1	0.0
General Disorders and Administration Site Conditions		
Fatigue	3.3	4.5
Pyrexia	3.0	0.0
Administration site reaction	1.3	0.5
Oedema peripheral	0.5	6.2
Asthenia	0.1	2.2
Infections and Infestations		
Influenza	5.2	0.5
Urinary tract infection	0.5	2.2
Upper respiratory tract infection	0.1	0.5
Musculoskeletal, and Connective Tissue Disorders		
Arthralgia	2.0	1.1
Back pain	1.3	0.5

	SALOFALK N=841 %	Placebo N=176 %
Nervous System Disorders		
Headache	6.7	11.3
Dizziness	1.7	2.8
Insomnia	0.1	1.7
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	2.0	2.8
Skin and Subcutaneous Tissue Disorders		
Rash	2.8	2.2
Spots	2.2	5.1
Pruritus	1.1	0.5
Alopecia	0.8	1.1

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during the post-approval use of SALOFALK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Agranulocytosis

Cardiac Disorders: Myocarditis, Pericarditis

Eye Disorders: Eye swelling

Gastrointestinal Disorders: Abdominal pain (upper, lower), Abdominal cramps, Abdominal distension, Abnormal faeces, Anal pruritus, Anorectal discomfort, Constipation, Diarrhoea, Faeces discoloured, Flatulence, Frequent bowel movements, Mucus stools, Nausea, Painful defecation, Pancreatitis, Proctalgia, Rectal discharge, Rectal tenesmus, Stomach discomfort, Vomiting

General Disorders and Administration Site Conditions: Fatigue, Medication residue, Pain, Pyrexia, Mesalamine-induced acute intolerance syndrome

Immune System Disorder: Anaphylactic reaction

Hepatobiliary Disorders: Hepatic impairment, including hepatic failure or hepatitis

Nervous System Disorders: Burning sensation, Dizziness, Headache, Intracranial hypertension

Renal and Urinary Disorders: Nephrolithiasis

Respiratory, Thoracic and Mediastinal Disorders: Allergic and fibrotic lung reactions Dyspnoea, Eosinophilic pneumonia, Interstitial alveolitis, Pleurisy

Skin And Subcutaneous Tissue Disorder: Alopecia, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Erythema, Photosensitivity, Pruritus, Rash, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Urticaria

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interaction between azathioprine, 6-mercaptopurine and aminosaliclates (including mesalamine) can increase the risk of leucopenia. Other potential interactions with a number of drugs could occur. See [9.4 Drug-Drug Interactions](#).

9.4 Drug-Drug Interactions

Interaction between azathioprine, 6-mercaptopurine and aminosaliclates including mesalamine, has been reported with oral mesalamine. Concomitant treatment with mesalamine can increase the risk of myelosuppression in patients receiving azathioprine or 6-mercaptopurine. An increase in whole blood 6-thioguanine nucleotide (6-TGN) concentrations has been reported although the mechanism of this interaction remains unclear.

Mesalamine could also increase renal and hematologic toxicity of methotrexate by additive effect and diminished absorption of folic acid.

The hypoglycemic effect of sulfonylureas may be enhanced. Interactions with coumarin, methotrexate, probenecid, sulfapyrazone, spironolactone, furosemide and rifampicin cannot be excluded. Potentiation of undesirable glucocorticoid effects on the stomach is possible.

A theoretical interaction of salicylates with Varicella Virus Vaccine (chicken pox vaccine) might increase the risk of Reye's syndrome; as a result, the use of salicylates (including mesalamine) is discouraged for six weeks following Varicella vaccination.

The concurrent use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of nephrotoxicity. Monitor patients using nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of mesalamine (5-aminosalicylic acid, 5-ASA), is not fully understood, but appears to be topical rather than systemic. Inflammatory intestinal disease is often accompanied by

diffuse tissue reactions including ulceration and cellular infiltration of lymphocytes, plasma cells, eosinophils, polymorphonuclear cells and activated phagocytic cells.

The interference of mesalamine with either leukotriene or prostaglandin metabolism may play a major role in suppressing the inflammatory response mechanism. 5-ASA prevents accumulation of thromboxane B₂ and 6-keto-prostaglandin F₁. Both 5-ASA and SAS reverse H₂O, and Cl⁻ secretion and increase Na⁺ secretion in experimentally-induced colitis in guinea pigs. SAS and 5-ASA are known to inhibit polymorphonuclear cell migration possibly via lipoxygenase inhibition at concentrations lower than those required to inhibit prostaglandin synthesis. It is thus possible that both SAS and 5-ASA are capable of inhibiting both pathways via lipoxygenase inhibition.

Intestinal secretion is stimulated not only by prostaglandins but also by the metabolites of arachidonic acid generated via the lipoxygenase pathway. Upon phagocytic activation and arachidonic acid metabolism activation, reactive oxygen metabolites are generated. 5-ASA acts as a dose dependent antioxidant which scavenges oxygen derived free radicals produced by activated phagocytes. In addition, 5-ASA associates with the membrane surface, allowing chain breaking anti-oxidant activity when peroxidation is initiated within the membrane. 5-ASA is able to block initiation of oxidation from solution as well as propagation within the membrane. 5-ASA also inhibits the formation of both eicosanoids and cytokines.

10.2 Pharmacodynamics

SALOFALK contains mesalamine 5-aminosalicylic acid (5-ASA), the active principle of the prodrug sulfasalazine. Although the 5-ASA mode of action is not clear, it appears to be multi-factorial. 5-ASA is thought to affect the inflammatory process through its ability to inhibit prostaglandin synthesis, interfere with leukotriene synthesis and consequent leukocyte migration as well as act as a potent scavenger of free radicals. Regardless of the mode of action, 5-ASA appears to be active mainly topically rather than systemically. Rectal administration as 500 or 1000 mg suppositories of mesalamine (5-aminosalicylic acid) allows for direct targeting of free 5-ASA to the sites of inflammation along the mucosal lumen of the rectum, sigmoid and distal large bowel.

Animal Studies

5-ASA (mesalamine) is the active moiety of the prodrug sulfasalazine which acts to suppress inflammatory bowel disease. Animal pharmacology tests were conducted on 5-ASA using the oral route of administration for most tests, at a dose of 500 mg/kg in order to simulate practice relevant conditions. No adverse effect of 5-ASA on the following parameters or in the following animal pharmacology tests could be established: tremorine antagonism, hexobarbital sleep time, motor activity, anticonvulsant action (metrazol and electric shock), blood pressure, heart rate, respiratory rate (up to 10 mg/kg, i.v.), tocolysis (antispasmodic assay), local anaesthesia, antihyperthermal and antipyretic effects. In the paw-edema test with carrageen injection, 200 mg/kg per os proved ineffective, but 500 mg/kg 5-ASA per os exhibited mild antiphlogistic action.

In the animal renal function tests (natriuresis and diuresis), no biologically relevant effects of 200 mg/kg per os were demonstrated. After 600 mg/kg, marked functional changes were observed: increases in total urinary output, natriuresis and proteinuria. The urinary sediment contained an increased number of erythrocytes and epithelial cells. Both potassium elimination and specific weight were reduced. It can be concluded from these experiments that even high doses of 5-ASA have no effect on vital parameters. Disturbances in renal function are to be expected only at dosages equivalent to a single dose at least 8 to 10 times the daily dose in man.

10.3 Pharmacokinetics

Absorption

Mesalamine (5-ASA) administered as a rectal suppository is variably absorbed. Systemic absorption of rectally administered 5-ASA is low as shown by urinary recoveries which range from 5% to 35% of the daily dose administered. In patients with ulcerative colitis treated with mesalamine 500 mg rectal suppositories, administered once every eight hours for six days, the mean mesalamine peak plasma concentration (C_{max}) was 353 ng/mL (CV=55%) following the initial dose and 361 ng/mL (CV=67%) at steady state. The mean minimum steady state plasma concentration (C_{min}) was 89 ng/mL (CV=89%). Absorbed mesalamine does not accumulate in the plasma.

Distribution:

Mesalamine administered as rectal suppositories distributes in rectal tissue to some extent. In patients with ulcerative proctitis treated with mesalamine 1000 mg rectal suppositories, rectal tissue concentrations for 5-ASA and N-acetyl-5-ASA have not been rigorously quantified.

Metabolism:

Mesalamine is extensively metabolized by acetylation. The only major metabolite of 5-ASA identified in man is N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The site of metabolism has not been elucidated. In patients with ulcerative colitis treated with one 500 mg mesalamine rectal suppository every eight hours for 6 days, peak concentrations (C_{max}) of N-acetyl-5-ASA ranged from 467 ng/mL to 1399 ng/mL following the initial dose and from 193 ng/mL to 1304 ng/mL at steady state.

The influence of renal and hepatic impairment on pharmacokinetics of mesalamine has not been evaluated.

Elimination

Mesalamine is eliminated from plasma mainly by urinary excretion, predominantly as N-acetyl-5-ASA. In patients with ulcerative proctitis treated with one mesalamine 500 mg rectal suppository every eight hours for six days, $\leq 12\%$ of the dose was eliminated in urine as unchanged 5-ASA and 8-77% as N-acetyl-5-ASA following the initial dose. At steady state, $\leq 11\%$ of the dose was eliminated as unchanged 5-ASA and 3-35% as N-acetyl-5-ASA. The mean elimination half-life was five hours (CV=73%) for 5-ASA and six hours (CV=63%) for N-acetyl-5-ASA following the initial dose. At steady state, the mean elimination half-life was seven hours for both 5-ASA and N-acetyl-5-ASA (CV=102% for 5-ASA and 82% for N-acetyl-5-ASA).

11 STORAGE, STABILITY AND DISPOSAL

SALOFALK must be stored below 25°C. Can be refrigerated. Keep away from direct heat, light and humidity.

Disposal of SALOFALK should be in keeping with recommendations governing the disposal of pharmaceutical waste.

12 SPECIAL HANDLING INSTRUCTIONS

Avoid excessive handling of suppository, which is designed to melt at body temperature. SALOFALK will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

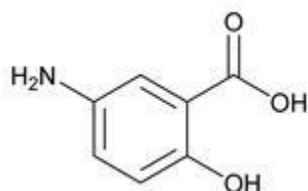
Drug Substance

Proper name: 5-aminosalicylic acid, mesalamine

Chemical name: 5-aminosalicylic acid (5-ASA)

Molecular formula and molecular mass: C₇H₇NO₃ 153.14

Structural formula:



Physicochemical properties:

Description: 5-aminosalicylic acid is a light tan to pink, needle shaped, crystalline powder.

Solubility: Slightly soluble in water, very slightly soluble in methanol and practically insoluble in chloroform; soluble in diluted HCl and diluted alkali hydroxides.

Melting Range: 272°-280°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Ulcerative proctitis

Table 3 Summary of patient demographics for clinical trials in active proctitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (years)	Sex
Study 1	double-blind, placebo-controlled multicenter study	500 mg mesalamine three times daily (1.5 g/day) Rectal suppository 6 weeks	n = 39	39 (17 to 73)	34 M / 45 F
		placebo	n = 40		

A double-blind, placebo-controlled multicenter study was conducted in North America in patients with mild to moderate active proctitis. The primary measures of efficacy were clinical disease activity index

[DAI], sigmoidoscopic and histological evaluations. The dosage regimen: was 500 mg mesalamine three times daily (1.5 g/day). A total of 79 patients were studied (39 patients received mesalamine suppositories, and 40 patients received placebo). Patients were evaluated clinically and sigmoidoscopically after three and six weeks of suppository treatment. Patients were 17 to 73 years of age (mean = 39 years), 57% were female, and 97% were white. Patients had an average extent of proctitis (upper disease boundary) of 10.8 cm and 84% of patients had multiple prior episodes of proctitis.

Study Results

Study 1: Compared to placebo, mesalamine suppository treatment was statistically ($p < 0.01$) superior with respect to improvement in stool frequency, rectal bleeding, mucosal appearance, and disease severity. Mesalamine-treated patients had an 80.4% mean reduction in DAI ($p < 0.05$) compared to placebo (36.8%) and 84.4% of mesalamine patients were considered 'much improved' by the investigator ($p < 0.01$) at 6 weeks. Daily diary records revealed a significant improvement in rectal bleeding in the mesalamine-treated patients ($p < 0.05$) within the first week compared to placebo indicating a faster onset of action. The effectiveness of mesalamine suppositories was statistically significant irrespective of sex, extent of proctitis, duration of current episode or duration of disease.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Animal studies to date show the kidney to be the only significant target organ for 5-ASA toxicity in rats and dogs. At high doses, the lesions produced consisted of papillary necrosis and multifocal proximal tubular injury. In rats, the no-effect levels were 160 mg/kg/day for females and 40 mg/kg/day for males (minimal and reversible tubular lesions seen) after 13 weeks of oral administration. In dogs, the no-effect level in both males and females was 40 mg/kg/day after 6 months of oral administration. In this six-month oral toxicity study in dogs, doses of 80 mg/kg/day (about 1.4 times the recommended human intra-rectal dose, based on body surface area) and higher, caused renal pathology similar to that described for the rat. In a rectal toxicity study of mesalamine suppositories in dogs, a dose of 166.6 mg/kg (about 3.0 times the recommended human intra-rectal dose, based on body surface area) produced chronic nephritis and pyelitis. Aside from gastric lesions, heart lesions and bone marrow depression seen in some of the rats at the 640 mg/kg level and considered secondary effects of kidney damage, no other signs of systemic toxicity were noted at daily doses up to 160 mg/kg in rats and 120 mg/kg in dogs for 13 weeks and six months, respectively.

In the 12-month oral toxicity study in dogs, keratoconjunctivitis sicca (KCS) occurred at oral doses of 40 mg/kg/day (about 0.72 times the recommended human intra-rectal dose, based on body surface area) and above.

Carcinogenicity: Administration of doses of 0, 50, 100 and 320 mg/kg/day for 127 weeks in rats did not result in significant differences in unscheduled deaths, clinical signs, nodules or masses, between groups. Ophthalmoscopic investigations revealed no treatment-related changes. Treatment with SALOFALK was not associated with oncogenic changes or an increased tumor risk. The assessment of hematology, clinical biochemistry and urinalysis indicated no changes of toxicological significance at 13, 26 and 52 weeks of treatment.

After 127 weeks, analysis of the lesions indicated slight substance-related and dose-dependent toxic changes as degenerative kidney damage and hyalinization of tubular basement membrane and Bowman's capsule in the 100 mg and 320 mg/kg/day groups. Ulceration of the gastric mucosa and atrophy of the seminal vesicles were also more frequent in the 320 mg/kg/day group.

Genotoxicity: 5-ASA was not mutagenic in the Ames test, *E. coli* reverse mutation assay, mouse micronucleus test, sister chromatid exchange assay, or in a chromosomal aberrations assay. In contrast, sulfapyridine, which is the other primary metabolite of salicylazosulfapyridine, has tested positive in certain mutagenicity tests.

Reproductive and Developmental Toxicology: Teratology studies with 5-ASA have been performed in rats at oral doses up to 320 mg/kg/day and in rabbits at oral doses up to 495 mg/kg/day (about 1.7 and 5.4 times the recommended human intra-rectal dose, respectively). The battery of tests completed to date has shown that 5-ASA is devoid of embryotoxicity and teratogenicity in rats and rabbits; that it does not affect male rat fertility after five weeks of oral administration at 296 mg/kg/day; and that it lacks the potential to affect late pregnancy, delivery, lactation or pup development in rats.

Other Studies

Nephrotoxic potential of 5-aminosalicylic acid: Owing to its structural relationship to phenacetin, the aminophenols and salicylates, 5-ASA was included in a series of compounds studied following identification of antipyretic-analgesic nephropathy in humans. Calder *et al.* has reported in rats that in addition to the proximal tubule necrosis seen with acetylsalicylic acid (e.g. Aspirin®) and phenacetin derivatives, 5-ASA produced papillary necrosis, following single intravenous doses ranging from 150 mg/kg to 872 mg/kg.

Diener *et al.* have shown that oral doses of 5-ASA of 30 mg/kg and 200 mg/kg daily for four weeks failed to produce any adverse effects on kidney function or histology in rat.

In a 13-week rat study, there were no renal lesions after four weeks in the animals receiving up to 160 mg/kg orally per day, but severe papillary necrosis and proximal tubular injury were seen in most animals receiving 640 mg/kg orally per day. At 13 weeks, the female animals were free of pathology up to 160 mg/kg; minimal and reversible lesions in the tubules occurred in a few males (with no changes in renal function) at the 40 mg/kg/day level. After six months of oral administration in dogs, no toxicity was seen in the 40 mg/kg/day group. At 80 mg/kg/day, two of eight treated dogs showed slight to moderate renal papillary necrosis. These dogs as well as two others showed minimal to moderate tubular lesions. At 120 mg/kg/day, two females had slight papillary necrosis. These and two others showed minimal to moderate tubule injury.

5-ASA rectal irritation challenge in dogs: A rectal mucosa irritation study was designed and conducted to determine if 5-ASA rectal suspension causes any mucosal tissue stress either histologically or macroscopically. The test was carried out blind against placebo, administering one rectal suspension per day.

Treated dogs (n = 10) received 2.0 g of 5-ASA which was retained for an average of 5.5 hours over the 27-day study. The placebo group (n = 6) received suspensions of the same vehicle composition, but without 5-ASA. Calcium carbonate and food colouring were used in place of 5-ASA to mimic its appearance in the suspension formula. The rectal suspension control group (n = 2) received physiological saline enemas of equivalent volume daily. Seven days prior to dosing and after Days 15 and 30, all animals were given a proctologic examination with rectal biopsy. The histopathology data revealed no signs of significant irritation in either the treated or the control group. There was an increased incidence of edema of the lamina propria of the rectum in both the treated and control

groups. These lesions represent the mildest form of inflammation normally expected in the rectum. This mucosal inflammation is a completely reversible alteration and is probably the result of mild superficial irritation. There was no significant difference in the incidence and or severity of these changes between the treated and control groups.

The anorectal examination data revealed no signs of irritation in either treated or control group animals. The amount of mucus present in the rectum increased with time in all dogs but did not exceed minimal severity. There was no significant difference between treated and control groups in the incidence and/or degree of severity of anorectal examination.

In conclusion, these data indicated no significant rectal mucosal tissue irritation in dogs related to the daily rectal administration of 2 g of 5-aminosalicylic acid rectal suspension over a period of 27 days.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **SALOFALK**[®]

Mesalamine suppositories

Read this carefully before you start using **SALOFALK** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SALOFALK**.

What is SALOFALK used for?

SALOFALK is used:

- to manage a condition called ulcerative proctitis, in which the rectum is inflamed.
- as a combination therapy for severe inflammation of the lining of the large bowel and rectum (distal ulcerative colitis).

How does SALOFALK work?

SALOFALK is believed to reduce the activity of certain chemicals in your body that cause inflammation (e.g., prostaglandins). This helps to reduce the swelling and pain in your rectum and lower part of your large bowel.

What are the ingredients in SALOFALK?

Medicinal ingredients: mesalamine (me-SAL-a-meen), also known as 5-aminosalicylic acid, 5-ASA or mesalazine.

Non-medicinal ingredients: Witepsol H-15 (suppository wax base).

SALOFALK is gluten-free and phthalate-free.

SALOFALK comes in the following dosage forms:

Suppositories: 500 mg or 1000 mg.

Do not use SALOFALK if:

- you have severe kidney problems
- you have severe liver problems
- you are allergic to mesalamine or to any of the non-medicinal ingredients in SALOFALK, or component of the container (see **What are the ingredients in SALOFALK?**)
- you have a sensitivity to a family of drugs known as salicylates, which includes acetylsalicylic acid (ASA)

- you have stomach or small intestinal ulcers
- you have a blockage in your urinary tract
- the patient is an infant under two years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use SALOFALK. Talk about any health conditions or problems you may have, including if you:

- have any kidney or liver problems
- have heart problems, including a history of heart inflammation (which may be the result of an infection of the heart)
- have stomach pain
- have had an unusual or allergic reaction to sulfasalazine (SAS), an ingredient in medicines used to treat ulcerative colitis
- have bleeding or clotting problems

Other warnings you should know about:

Serious Side Effects: SALOFALK can cause serious side effects:

- **Serious skin reactions:** Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and toxic epidermal necrolysis (TEN) have happened in people taking SALOFALK. These skin reactions are serious. Stop taking SALOFALK and get immediate medical help if you experience any signs of a severe skin reaction, such as mouth sores, a severe skin rash, or any other signs of an allergic reaction.
- **Kidney problems, including kidney stones:** People taking SALOFALK can develop kidney stones or other kidney problems. Symptoms may include blood in the urine, urinating more often and pain in your back, side, belly or groin. Be sure to drink enough liquids while you are using SALOFALK. Talk to your healthcare professional about how much water or other liquids you should be drinking.
- **Acute Intolerance Syndrome:** Symptoms of acute intolerance syndrome can be similar to a flare of your condition. If you think you are experiencing a flare, talk to your healthcare professional immediately.
- **Heart problems:** These include inflammation of the heart muscle (myocarditis) and inflammation of the tissue around the heart (pericarditis).
- **Blood problems:** This includes low numbers of all types of blood cells (myelosuppression).
- **Liver problems:** This included liver failure.

For more information on these and other serious side effects see the **Serious side effects and what to do about them** table, below.

Pregnancy and Breastfeeding:

- Talk to your healthcare professional if you are pregnant or thinking of becoming pregnant.
- You should not breastfeed while you are taking SALOFALK. SALOFALK passes into breastmilk.
- If you breastfeed your baby while taking SALOFALK, your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your healthcare professional

right away if they have diarrhea. Your healthcare professional may advise you to stop breastfeeding your baby.

Sensitivity to the sun: Tell your healthcare professional if you have eczema or atopic dermatitis. Your skin may be more sensitive to sunlight when taking SALOFALK. You should avoid the sun and wear protective clothing and a broad-spectrum sunscreen when you are outdoors.

Blood tests: SALOFALK can cause abnormal blood test results. Your healthcare professional will do blood tests before you start taking SALOFALK and periodically during treatment. They will check the health of your liver and kidneys as well as the levels of your red and white blood cells and monitor you for other side effects. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SALOFALK:

- other medicines used to treat ulcerative colitis, such as azathioprine, 6-mercaptopurine, aminosaliculates
- sulfonyleureas, used to treat diabetes
- anti-inflammatory drugs (NSAIDS), used to treat pain and inflammation
- anticoagulants, used to thin the blood and prevent blood clots, such as coumarin
- methotrexate, used to treat cancer and severe inflammatory conditions
- medicines used to treat gout, such as probenecid, sulfipyrazone
- medicines used to treat high blood pressure, such as spironolactone, furosemide
- rifampicin, an antibiotic used to treat bacterial infections
- the chicken pox vaccine (varicella virus vaccine)

How to use SALOFALK:

- Take SALOFALK exactly as your healthcare professional has told you. Your healthcare professional will tell you how many SALOFALK suppositories to use. They may adjust your dose as needed. Do not stop using SALOFALK without talking to your healthcare professional.
- Detach one suppository from the strip of suppositories.
- Hold the suppository upright and carefully remove the plastic wrapper.
- Avoid touching the suppository for too long. This is because the suppository can melt at body temperature.
- Insert the pointed end of the suppository completely into your rectum. Insert it with gentle pressure.
- You may use a small amount of lubricating gel on the tip of the suppository to help with the insertion. Keep the suppository in your rectum for one to three hours or longer, if possible.

Usual dose:

500 mg SALOFALK: one suppository, two or three times daily.

1000 mg SALOFALK: one suppository, once daily, at bedtime.

The usual adult dose is 1000 mg - 1500 mg per day.

Overdose:

If you think you, or a person you are caring for, have used too much SALOFALK, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of SALOFALK, use it as soon as possible, unless it is almost time for the next dose. Do not use two doses at the same time to make up for a missed dose.

What are possible side effects from using SALOFALK?

These are not all the possible side effects you may have when using SALOFALK. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- anorectal pain, discomfort or discharge
- anal itching
- stomach pain, cramps or discomfort
- nausea, vomiting
- bloating, gas
- constipation
- diarrhea
- painful or incomplete bowel movements
- abnormal stool (frequent bowel movements, stools discoloured, mucous in stool)
- dizziness
- fever
- flu like symptoms
- hemorrhoids
- hair loss
- headache
- inflammation/swelling of the throat
- itching, rash, skin redness
- joint and lower back pain
- reaction at site of administration
- sleeplessness

- swollen hands or lower legs
- tiredness or weakness
- cough
- difficulty breathing
- eye swelling
- medication residue
- pain

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop using drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Kidney stones (hard little pebbles that form in your kidneys): blood in urine, urinating more often, pain in your back, side, belly or groin		✓	
Urinary tract infection: strong, persistent urge to urinate, pain or burning when urinating, bloody, cloudy or strong smelling urine, passing frequent, small amounts of urine		✓	
UNKNOWN			
Pancreatitis (inflammation of the pancreas): abdominal pain, nausea, vomiting, fever, rapid heartbeat, feeling tired			✓
Allergic reaction: rash, hives, itching, fever, swelling of the mouth, lips, tongue or throat, difficulty in swallowing or breathing			✓
Heart problems (including myocarditis, pericarditis or heart inflammation): chest pain, fast or irregular heartbeat, fatigue, fever, difficulty in breathing, accumulation of fluid in the lung, cough			✓
Kidney problems (inflammation of the kidney or kidney failure): blood in the urine, fever, increased or decreased urine output, mental status changes (drowsiness, confusion, coma), rash,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop using drug and get immediate medical help
	Only if severe	In all cases	
swelling of the body, weight gain (from retaining fluid)			
Liver problems (including liver failure): severe abdominal pain, nausea, vomiting, yellowing of the skin and eyes, loss of appetite, bloating and distension, dark urine, pale stool			✓
Acute intolerance syndrome: cramping, stomach pain, bloody and excessive stools, fever, headache, rash			✓
Lung problems: difficulty in breathing, dry cough, fever, chills, sweating, body aches, generally feeling unwell			✓
Blood problems (low levels of one or more types of blood cells): fatigue, difficulty in breathing with exertion, rapid or irregular heartbeat, pale skin, frequent or prolonged infections, unexplained or easy bruising, nosebleeds, bleeding gums, prolonged bleeding from cuts, skin rash, dizziness, headache			✓
Serious skin reactions (SCAR, DRESS, SJS, TEN): reddish, flat circular patches with blisters on the skin or inside the mouth, eyes, nose, or genitals, fever, severe rash, peeling skin, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often			✓
Pleurisy (accumulation of fluid in the lungs): dry cough, chest pain, difficulty in breathing			✓
Increased pressure in brain: headache which may originate behind your eyes and worsen with eye movements, with blurred or dimmed vision, double vision, seeing light flashes, difficulty seeing to the side, and brief or permanent vision loss, dizziness, nausea, vomiting, ringing in ears			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop using drug and get immediate medical help
	Only if severe	In all cases	
Worsening of ulcerative colitis: worsening of stomach cramps or pain or diarrhea		✓	
Photosensitivity (sensitivity of the skin to the sun): rash, redness, blisters, itching and burning when the skin is exposed to the sun or UV light	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

SALOFALK must be stored below 25°C. Can be refrigerated. Keep away from direct heat, light and humidity.

Keep out of reach and sight of children.

NOTE: SALOFALK will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel.

If you want more information about SALOFALK:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

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