PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSALOFALK®

Mesalamine Suppositories
500 mg and 1000 mg

LOWER GASTROINTESTINAL TRACT ANTI-INFLAMMATORY

A07EC02

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RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS, FEB 2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SALOFALK® (mesalamine suppositories) 500 and 1000 mg are indicated:

- in the 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

Clinical studies with SALOFALK® have not been performed in the geriatric population.

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 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

SALOFALK® is contraindicated in:

- patients with severe renal impairment (GFR<30ml/min/1.73m^2) and/or severe hepatic impairment (see WARNINGS AND PRECAUTIONS).
- cases of existing gastric or duodenal ulcer.
- patients with urinary tract obstructions.
- infants under two years of age.
- patients hypersensitive to salicylates, including acetylsalicylic acid (e.g. Aspirin®), may also be hypersensitive to this medication.

3 DOSAGE AND ADMINISTRATION

3.1 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 INDICATIONS)

3.2 Administration

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.

3.3 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.

4 OVERDOSAGE

There has been no clinical experience with mesalamine overdosage. However, because mesalamine is an aminosalicylate, 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.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – 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).

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

SALOFALK® is gluten-free and phthalate-free.

6 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 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-ASA/Mesalazine products. Therefore, SALOFALK® (mesalamine suppositories) is contraindicated in patients with severe hepatic impairment (see

Contraindications). In patients with mild to moderate liver function impairment, caution should be exercised and SALOFALK® (mesalamine suppositories) 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 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.

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.

6.1 Special Populations

6.1.1 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 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.

6.1.2 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 as hypersensitivity reactions manifested as diarrhoea in the infants have been reported.

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

6.1.3 Pediatrics

Information on the safety and efficacy of SALOFALK® in children is limited.

SALOFALK® should not be used in infants/toddlers aged less than 24 months.

6.1.4 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.

7 ADVERSE REACTIONS

7.1 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.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

Table 1: Clinical Trial Adverse Events Reported in > 0.1% of Patients

SYSTEM ORGAN CLASS Preferred Term	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
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

7.3 Post-Market Adverse Reactions

The following adverse reactions have been identified during the post-approval use of SALOFALK® suppository. 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

Hepatobilary Disorders: Hepatic impairment, including hepatic failure or hepatitis

Nervous System Disorders: Burning sensation, Dizziness, Headache

Renal and Urinary Disorders: Nephrolithiasis

Respiratory, Thoracic And Mediastinal Disorders: Dyspnoea, eosinophilic pneumonia, interstitial alveolitis, allergic and fibrotic lung reactions

Skin And Subcutaneous Tissue Disorder: Alopecia, Erythema, Pruritus, Rash, Urticaria

The following adverse events have been identified during the post-approval use of mesalamine products:

Immune System Disorder: Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Skin And Subcutaneous Tissue Disorder: Stevens-Johnson Syndrome (SJS)

8 DRUG INTERACTIONS

8.1 Overview

Interaction between azathioprine, 6-mercaptopurine and aminosalicylates (including mesalamine) can increase the risk of leucopenia. Other potential interactions with a number of drugs could occur (see Drug-Drug Interactions).

8.2 Drug-Drug Interactions

Interaction between azathioprine, 6-mercaptopurine and aminosalicylates 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, sulfinpyrazone, 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.

8.3 Drug-Food Interactions

Drug-food interactions have not been studied.

8.4 Drug-Herb Interactions

Drug-herb interactions have not been studied.

8.5 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.

8.6 Drug-Lifestyle Interactions

Drug-lifestyle interactions have not been studied.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The mechanism of action of mesalamine (5-aminosalisylic 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 H_2O, 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.

9.2 Pharmacodynamics

SALOFALK® contains mesalamine (5-aminosalisylic 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.

9.3 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 adminstered. 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, ≤ 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, ≤

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).

10 STORAGE, STABILITY AND DISPOSAL

SALOFALK® must be stored below 25°C (77ºF). Can be refrigerated. Keep away from direct heat, light and humidity.

11 SPECIAL HANDLING INSTRUCTIONS

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

12 PHARMACEUTICAL INFORMATION

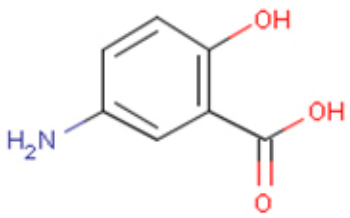
Drug Substance

Proper name: 5-aminosalicylic acid, mesalamine

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

Molecular formula and molecular mass: $C_7H_7NO_3$ 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

13 CLINICAL TRIALS

13.1 Study Results

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.

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.

14 NON-CLINICAL TOXICOLOGY

DETAILED PHARMACOLOGY

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 specify 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.

Human Studies

See ACTION AND CLINCAL PHARMACOLOGY**.**

TOXICOLOGY

Long-term Toxicity

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.

Mutagenicity
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.

Reproduction Studies
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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr SALOFALK®
Mesalamine Suppositories
500 mg, 1000 mg

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® suppositories are 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® Suppositories are gluten-free and phthalate-free.

SALOFALK® comes in the following dosage forms:

Suppositories: 500 mg or 1000 mg.

Do not use SALOFALK® if:

- You are a patient with severe kidney (renal) problems and/or severe liver (hepatic) problems
- You are allergic to mesalamine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container
- You have a sensitivity to salicylates, for example acetylsalicylic acid (Aspirin®)
- 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 a pre-existing liver disease. There have been reports of liver failure and increased

liver enzymes in patients treated with 5-ASA or mesalazine (=mesalamine) products
- have inflammation of the heart muscle and lining around the heart. Your healthcare professional will decide if this product is right for you.
- have stomach pain
- have mild to moderate problems with your liver function. Your healthcare professional will decide if this product is right for you.
- ever had any unusual or allergic reaction to sulfasalazine (SAS)
- have mild to moderate problems with your kidney. Your healthcare professional will decide if this product is right for you.
- have bleeding or clotting disorders
- have higher than normal blood urea nitrogen (BUN) levels (kidney function test)
- have higher than normal serum creatinine levels (kidney function test)
- have higher than normal proteins in your urine (proteinuria)
- are pregnant or breastfeeding. Mesalamine is excreted in human breast milk. Your healthcare professional will decide if this product is right for you.

WHILE using SALOFALK®:
- Discontinue use at first sign of rash or fever.

Your healthcare professional may test your blood or urine regularly to monitor your kidney function. This is because prolonged use of SALOFALK® may damage your kidneys.

Other warnings you should know about:
Kidney stones may develop with use of mesalazine. Symptoms may include blood in 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.

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®:
Interaction between azathioprine, 6-mercaptopurine, sulfonylureas, anti-inflammatory drugs (NSAIDS) and aminosalicylates (such as SALOFALK®) has been reported.

Drug interactions with coumarin, methotrexate, probenecid, sulfinpyrazone, spironolactone, furosemide, rifampicin and Varicella Virus Vaccine (chicken pox vaccine) may be possible.

How to use SALOFALK®:

Patient Instructions:
- Detach one suppository from the strip of suppositories.
- Hold 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. This will help achieve the maximum benefit.

Your healthcare professional may adjust your dose as needed. Do not stop using the suppositories without discussing it with your healthcare professional first.

Usual dose:
One 500 mg SALOFALK® suppository, two or three times daily.
One 1000 mg SALOFALK® suppository once daily, at bedtime.

The usual adult dose is 1.0 - 1.5 g per day.

Your healthcare professional will tell you exactly how much SALOFALK to use.

Overdose:

If you think you have used too much SALOFALK®, contact your 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 feel when using SALOFALK®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects reported with SALOFALK® suppositories during clinical trials include:

- anorectal pain or discomfort
- bloating
- constipation
- diarrhoea
- dizziness
- fever
- flu like symptoms
- haemorrhoids
- hair loss
- having gas (flatulence)
- headache
- inflammation/swelling of the throat
- itching
- joint and lower back pain
- nausea
- rash
- reaction at site of administration
- sleeplessness
- stomach pain

- swollen hands or lower legs
- tiredness or weakness
- urinary tract infection

Side effects identified with post-marketing use of SALOFALK® suppositories include:

- abnormal stool (frequent bowel movements, stools discoloured)
- anal itching
- cough
- difficulty breathing
- eye swelling
- feeling of incomplete or painful defecation
- hives
- medication residue
- mucus in stools
- pain
- painful bowel movements
- redness of the skin
- rectal pain and discharge
- stomach cramps or discomfort
- vomiting

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			
Chest Pain			✓
Kidney stones (hard little pebbles that form in your kidneys): blood in urine, urinating more often and pain in your back, side, belly or groin.		✓	
UNKNOWN			
Pancreatitis (inflammation of the pancreas): abdominal pain, nausea, vomiting, fever, rapid heartbeat, and feeling tired.			✓
Allergic reaction (hypersensitivity): rash, itching, fever, swelling of the mouth and throat, and difficulty in breathing.			✓
Myocarditis/ Pericarditis (inflammation of the heart muscle and lining around the heart): pain in the chest, abnormal heartbeat, fatigue, fever, difficulty in breathing, accumulation of fluid in the lung, and coughing.			✓

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	
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, swelling of the body, weight gain (from retaining fluid).			✓
Liver problems/Hepatitis (inflammation of the liver)**:** severe abdominal pain, nausea, vomiting, yellowing of the skin and eyes, drop in appetite, bloating and distension.			✓
Acute intolerance syndrome: cramping, stomach pain, bloody and excessive stools, fever, headache and rash.			✓
Interstitial pneumonia (lung abnormality with scarring): difficulty in breathing, dry cough, fever, and persistent unwell feeling.			✓
Blood problems/ Agranulocytosis/Aplastic anaemia (shortage 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 and bleeding gums, prolonged bleeding from cuts, skin rash, dizziness, and headache.			✓
Serious skin conditions (DRESS and SJS): swelling of the skin or serious rash seen as severe blisters of the skin and mucous membranes.			✓
Pleurisy (accumulation of fluid in the lungs): dry cough, chest pain, difficulty in breathing.			✓
Worsening of ulcerative colitis: worsening of stomach cramps or pain or diarrhoea.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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/adverse-reaction-reporting.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® suppositories must be stored below 25°C (77°F). Can be refrigerated. Keep away from direct heat, light and humidity.

Keep out of reach and sight of children.

NOTE: SALOFALK® suppositories 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.allergan.ca, or by calling 1-800-668-6424.

This leaflet was prepared by Aptalis Pharma Canada ULC.

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