

PRODUCT MONOGRAPH

Pr **SALOFALK**[®]

Mesalamine Rectal Suspension USP
2 g/60 g, 4 g/60 g

LOWER GASTROINTESTINAL TRACT ANTI-INFLAMMATORY

A07EC02

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PrSALOFALK®

Mesalamine Rectal Suspension USP
2 g/60 g, 4 g/60 g

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Rectal	Suspension 2 g/60 g and 4 g/60 g	potassium metabisulfite <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

SALOFALK® (mesalamine rectal suspension) 4 g/60 g is indicated:

- in the management of distal ulcerative colitis (DUC) extending to the splenic flexure including refractory DUC defined to include patients who are difficult to manage with conventional therapies and patients who are allergic to sulfasalazine (SAS).
- as adjunctive therapy in more extensive disease as well as for the prevention of relapse in distal ulcerative colitis.

SALOFALK® rectal suspension, 2 g/60 g is indicated:

- for the prevention of relapse in distal ulcerative colitis.

Geriatrics

Clinical studies with SALOFALK® rectal suspension, 2 g/60 g and 4 g/60 g, have not been performed in the geriatric population.

Pediatrics

Information on the safety and efficacy of SALOFALK® rectal suspension, 2 g and 4 g, in children is limited. Use of the drug should be limited to situations where a clear benefit is expected. SALOFALK® rectal suspension should not be used in infants under two years of age.

CONTRAINDICATIONS

SALOFALK® (mesalamine rectal suspension) is contraindicated in:

- patients with severe renal impairment ($GFR < 30 \text{ ml/min/1.73m}^2$) and/or severe hepatic impairment (see WARNINGS AND PRECAUTIONS).
- patients who are hypersensitive to this drug or to any ingredient in the formulation or

component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- 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.

WARNINGS AND PRECAUTIONS

General

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 rectal suspension) 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 rectal suspension) should only be used if the expected benefit clearly outweighs the risks to the patients.

SALOFALK[®] (mesalamine rectal suspension) 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-mercaptopurine¹⁻³.

Effects on Ability to Drive and Use Machinery

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

Carcinogenesis and Mutagenesis

Carcinogenicity studies in animals and mutagenicity tests were negative (See TOXICOLOGY)⁴.

Cardiovascular

Cardiac side effects, including pericarditis and myocarditis have been uncommonly reported with the use of mesalamine⁵.

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^{6,7}.

Gastrointestinal

Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or SAS therapy (18%)⁸, should be investigated in order to exclude pericarditis and pancreatitis either as adverse drug reactions to mesalamine or secondary manifestations of inflammatory bowel disease.

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[®] (mesalamine rectal suspension) is contraindicated in patients with severe renal impairment (see Contraindications). In patients with mild to moderate renal dysfunction, caution should be exercised and SALOFALK[®] (mesalamine rectal suspension) should be used only if the benefits outweigh the risks.

Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with a 100% mesalamine 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 signs of rash or pyrexia become apparent. In case of an allergic reaction, appropriate measures (standard of care) should be taken.

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.

Special Populations

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^{1,9}.

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

Nursing Women

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 milk⁹⁻¹². 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^{1,13-15}.

Pediatrics

Information on the safety and efficacy of SALOFALK[®] 2 g and 4 g rectal suspensions in children is limited. Use of the drug should be limited to situations where a clear benefit is expected.

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

Geriatrics

Clinical studies of mesalamine did not include sufficient numbers 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 or 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypersensitivity reactions have been reported in a sub-group of patients known to be allergic to sulfasalazine including rash¹⁶⁻¹⁹, pyrexia¹⁶⁻¹⁹, and dizziness^{16,18} with reactions occurring at the onset of therapy and resolving promptly following discontinuation^{16,17}.

Other manifestations of hypersensitivity reported with mesalamine include acute pancreatitis^{19,20}, hepatitis¹⁹, pericarditis, interstitial nephritis, interstitial pneumonia and pleural effusion. Interstitial pneumonia, pancreatitis and pericarditis have also been reported as manifestations of

inflammatory bowel disease²².

As with all 5-ASA products, exacerbations of ulcerative colitis characterized by cramping¹⁸, acute abdominal pain¹⁸⁻²⁰ and diarrhoea^{18,19,21} have been reported with mesalamine.

Other reported side effects include headache^{18,19,21,23}, flatulence¹⁸, nausea^{18,19,21,23}, and hair loss^{17,18}, 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.

Clinical Trial Adverse Drug 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 drug 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, Connective Tissue and Bone 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

SYSTEM ORGAN CLASS Preferred Term	SALOFALK® N=841 %	Placebo N=176 %
Spots	2.2	5.1
Pruritus	1.1	0.5
Alopecia	0.8	1.1

Post-Market Adverse Drug Reactions

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

Cardiac Disorders: Myocarditis

Gastrointestinal Disorders: Abdominal pain (upper, lower), Abdominal cramps, Abdominal discomfort, Constipation, Diarrhoea, Faeces discoloured (pale), Flatulence, Rectal tenesmus

General Disorders and Administrative Site Disorders: Fatigue, Medication residue, Pyrexia

Musculoskeletal and Connective Tissue Disorders: Back pain, Neck pain

Nervous System Disorders: Dizziness, Headache

Renal and Urinary Disorders: Chromaturia, Nephrolithiasis

Skin and Subcutaneous Tissue Disorders: Acute febrile neutrophilic dermatosis, Pruritus, Rash (erythematous, papular), Urticaria

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

Blood and Lymphatic System Disorders: Agranulocytosis

Immune System Disorder: Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS)

DRUG INTERACTIONS

Overview

Interaction between azathioprine, 6-mercaptopurine and aminosaliclates (including mesalamine) can increase the risk of leucopenia¹⁻³. Other potential interactions with a number of drugs could occur (see Drug-Drug Interactions).

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 unclear¹⁻³.

Mesalamine could also increase renal and hematologic toxicity of methotrexate by additive effect and diminished absorption of folic acid²⁴.

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^{1,25}.

Drug-food, drug-herb, or drug-laboratory interactions have not been studied.

Drug-Laboratories 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.^{56, 57, 58}

DOSAGE AND ADMINISTRATION

Dosing Considerations

Information on the safety and efficacy of SALOFALK[®] (mesalamine rectal suspension) 2 g/60 g and 4 g/60 g in children is limited. Use of the drug should be limited to situations where a clear benefit is expected.

Recommended Dose and Dosage Adjustment

Acute episodes:

SALOFALK[®] rectal suspension 4 g/60 g is self-administered on a daily basis during acute episodes of disease. Usually one unit-dose rectal suspension (4 g 5-ASA) is taken upon retiring and retained during the entire rest period. Best results are expected with prolonged retention.

The usual course of therapy for an adult is one unit of 4 g/60 g daily at bedtime. Response to treatment and adjustment in dosing frequency should be determined by periodic examination, including endoscopy and the assessment of symptomatology including rectal bleeding, stool frequency, and general well-being.

Daily dosing is continued until a significant response is achieved or the patient achieves remission.

Prevention of relapses:

SALOFALK[®] rectal suspension, 2 g/60 g is self-administered in the same manner on a daily basis to prevent relapse.

If, alternatively, the 4 g/60 g preparation is used to prevent relapse, the dose can usually be reduced to alternate days or every third day, depending upon disease activity. Abrupt

discontinuation of 5-ASA is not recommended. Dose tapering is recommended and each patient should be titrated to meet individual needs. Maintenance therapy is recommended to assure continued remission. However, should symptoms of diarrhoea and rectal bleeding recur, dosage should be increased to 4 g/60 g/day.

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 SALOFALK[®] doses at the same time to make up for a missed dose.

Administration

SALOFALK[®] rectal suspension, 4 g/60 g is self-administered on a daily basis during acute episodes of disease.

SALOFALK[®] rectal suspension, 2 g/60 g is self-administered in the same manner on a daily basis to prevent relapse.

OVERDOSAGE

There has been no clinical experience with mesalamine overdose. 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.

ACTION AND CLINICAL PHARMACOLOGY

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 cells²⁶.

The interference of mesalamine with either leukotriene or prostaglandin metabolism may play a major role in suppressing the inflammatory response mechanism²⁶⁻³². 5-ASA prevents accumulation of thromboxane B₂ and 6-keto-prostaglandin F₁²⁷. Both 5-ASA and SAS reverse H₂O, and Cl⁻ secretion and increase Na⁺ secretion in experimentally-induced colitis in guinea pigs³³. SAS and 5-ASA are known to inhibit polymorphonuclear cell migration possibly via lipoxygenase inhibition³² 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 inhibition²⁶.

Intestinal secretion is stimulated not only by prostaglandins but also by the metabolites of arachidonic acid generated via the lipoxygenase pathway^{26,32,34}. Upon phagocytic activation and arachidonic acid metabolism activation, reactive oxygen metabolites are generated³⁵. 5-ASA acts as a dose dependent³⁵ antioxidant which scavenges oxygen derived free radicals produced by activated phagocytes^{26,36}. 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 membrane³⁷. 5-ASA also inhibits the formation of both eicosanoids and cytokines^{26,36}.

Pharmacodynamics

SALOFALK[®] rectal suspension contains mesalamine (5-aminosalicylic acid, 5-ASA), the active principle of the prodrug sulfasalazine^{17,38-42}. 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 synthesis²⁷⁻³², interfere with leukotriene synthesis and consequent leukocyte migration^{27,28} as well as act as a potent scavenger of free radicals²⁶. Regardless of the mode of action, 5-ASA appears to be active mainly topically rather than systemically^{43,44}.

Pharmacokinetics

Absorption

Systemic absorption of rectally administered 5-ASA (mesalamine) is low as shown by urinary recoveries which range from 5 % to 35% of the amount given⁴⁰. In contrast, oral administration of free 5-ASA leads to high systemic absorption with rapid absorption from the small intestine^{9,39,40}; however, this route of administration provides for a reduced chance of topical effectiveness in the distal bowel. Rectally administered 5-ASA thus acts locally on the recto-sigmoidal colon. Satisfactory dosages (4 g mesalamine rectal suspension) have reached the splenic flexure⁴⁵.

Distribution

Rectal administration 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. Free intraluminal 5-ASA is taken up by mucosal cells, where it is acetylated and inactivated as N-Ac-5-ASA⁴⁶. Following rectal dosing, both free 5-ASA and its inactive metabolite, N-Ac-5-ASA, can be found within 1-2 hours post administration in plasma^{41,47}.

Metabolism

5-ASA metabolism is metabolised by acetylation^{9,38}. The only major metabolite of 5-ASA identified in man is N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA)³⁸. Following rectal dosing, both free and acetylated forms can be found in plasma within 1-2 hours post administration^{41,47}. Usually plasma concentrations are low and do not exceed a maximum serum level of about 10 µg/mL at rectal daily doses of up to 4 grams^{48,49}. Peak plasma levels of rectally administered 5-ASA (4 g rectal suspension) are reached within 3 to 6 hours, with a value of 2.6 ± 2.3 µg/mL¹⁷. Plasma levels are therefore negligible approximately 24 hours after dosing¹⁷. Following mucosal absorption, passage through the liver results in further acetylation⁴⁶. These results are consistent with pharmacokinetic parameters as measured for 5-ASA and its metabolites determined in studies with solid oral dosage forms. In solid oral dosage studies, it has been determined that 5-

ASA and its metabolite N-Ac-5-ASA are short lived in the serum with a half-life reported between 0.5-1.5 hours and 5-10 hours, respectively⁴⁴; 5-ASA is partially absorbed, excreted rapidly ($t_{1/2} = 0.4 - 2.4$ hours^{44,48}), and partially recovered unchanged in the faeces⁴⁴.

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

Excretion

The kidneys excrete both free 5-ASA and acetylated forms (N-Ac-5-ASA) into the urine^{40,46}. Urinary clearance of absorbed drug occurs rapidly, mainly as the acetylated metabolite. The recovery rate in urine varies between 8 and 17 percent of the administered rectal dose^{17,45}. Unabsorbed drug is excreted as the free and acetylated forms via faeces^{39,40,44}.

STORAGE AND STABILITY

SALOFALK[®] (mesalamine rectal suspension) is packaged in aluminum foil and should be stored at room temperature preferably under 25°C. Product expiration date and lot number are printed on the bottle base.

SPECIAL HANDLING INSTRUCTIONS

SALOFALK[®] (mesalamine rectal suspension) will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SALOFALK[®] (mesalamine rectal suspension) 2 g/60 g and 4 g/60 g are available as a unit of use rectal suspension. Non-medicinal ingredients include: carbomer, edetate disodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum.

SALOFALK[®] (mesalamine rectal suspension) is gluten- free and phthalate-free.

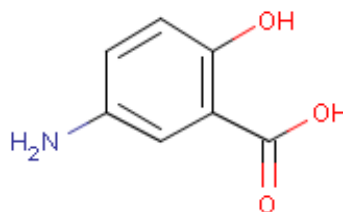
Each unit consists of a rectal dosing package designed for self-administration and disposal. A removable protective sheath covers the pre-lubricated suspension nozzle until ready for use. A one-way valve allows the suspension to flow from the bottle through the applicator nozzle and into the rectal vault as the patient squeezes the thin-walled collapsible bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	5-aminosalicylic acid, mesalamine	
Chemical name:	5-aminosalicylic acid (5-ASA)	
Molecular formula and molecular mass:	C ₇ H ₇ NO 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

CLINICAL TRIALS

In a 6-week, randomized, placebo-controlled, double-blind trial in 59 patients with ulcerative colitis, Sutherland *et al*, demonstrated the safety and efficacy of 4 g mesalamine rectal suspension. Twenty-nine (29) patients received the treatment drug and 30 patients received placebo. There was a significant improvement in disease symptoms in the treatment group ($p < 0.0001$) compared to the placebo group after 6 weeks of treatment. The mean disease activity index (DAI) decreased by 75% in the treatment group compared to 32% for placebo ($p < 0.05$). The rectal suspension was well tolerated with few and insignificant side effects⁵⁰.

In a separate study, the efficacy and safety of mesalamine rectal suspension 2g/60g and 4g/60g in the maintenance of remission were evaluated in a 6-month, randomized, double-blind trial in 29 patients who had ulcerative colitis. Before admission to the study, patients had participated in a placebo-controlled mesalamine rectal suspension study and had achieved a significant improvement in their disease activity or were in remission. Further significant declines in DAI were demonstrated for both dose groups during the first 3 months of therapy ($p < 0.001$). There was no significant difference in DAI scores between 3 and 6 months, or between the 2g/60g/day and 4g/60g/day doses. Two patients in the 2g/60g dose group and 3 patients in the 4g/60g dose group relapsed during the 6 month study period. Relapse rates did not differ significantly.⁴²

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 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.

Human Studies

See Action and Clinical 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 above⁵¹.

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 tests⁴.

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/kg⁵²⁻⁵⁴.

Diener *et al.*⁵⁵ 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.

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PART III: CONSUMER INFORMATION

PrSALOFALK®

Mesalamine Rectal Suspension USP

2 g/60 g, 4 g/60 g

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SALOFALK®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SALOFALK® rectal suspension, 4 g/60 g is used in the management of distal ulcerative colitis (inflammation of the lining of the large bowel and rectum) and may also be used in preventing the symptoms of the disease from recurring. SALOFALK® rectal suspension (4 g/60 g) can be used in combination with other drugs.

The lower strength of SALOFALK® rectal suspension, 2 g/60 g may also be used in preventing the symptoms of distal ulcerative colitis from recurring.

What it does:

SALOFALK® is believed to work by interfering in the activity of certain mediators of inflammation (e.g., prostaglandins) which helps reduce the inflammation (swelling and pain) in the rectum and lower part of the large bowel.

When it should not be used:

SALOFALK® should not be used if:

- patients with severe kidney (renal) impairment (GFR<30ml/min/1.73m²) and/or severe liver (hepatic) impairment (see WARNINGS AND PRECAUTIONS).
- You are allergic to mesalamine or to any ingredient in the formulation (see **What the non-medicinal ingredients are**)
- You have a sensitivity to salicylates, for example acetylsalicylic acid (Aspirin®)
- You have stomach or small intestinal ulcers
- You have urinary tract obstructions
- The patient is an infant under two years of age

What the medicinal ingredient is:

SALOFALK® contains mesalamine (me-SAL-a-meen), also known as 5-aminosalicylic acid, 5-ASA or mesalazine.

What the non-medicinal ingredients are:

SALOFALK® rectal suspension contains carbomer, edetate disodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum. SALOFALK® rectal suspension is gluten-free and phthalate-free.

What dosage forms it comes in:

SALOFALK® rectal suspensions, 2 g/60 g and 4 g/60 g are available for single-use. Each unit contains a rectal dosing package designed for self-administration and disposal. A removable protective sheath covers the pre-lubricated suspension nozzle until ready for use. A one-way valve allows the suspension to flow from the bottle through the applicator nozzle and into the rectum as the patient squeezes the thin walled collapsible bottle.

WARNINGS AND PRECAUTIONS

BEFORE you use SALOFALK® talk to your doctor or pharmacist if:

- You have a pre-existing liver disease. There have been reports of liver (hepatic) failure and increased liver enzymes in patients treated with 5-ASA or mesalazine (=mesalamine) products.
- You have mild to moderate liver function impairment. Your doctor will decide if this product is right for you.
- You ever had any unusual or allergic reaction to mesalamine (5-ASA), sulfasalazine (SAS), salicylates (Aspirin®), or sulphites
- You have liver or kidney disease
- You have bleeding or clotting disorders
- Your doctor has said you have higher than normal blood urea nitrogen (BUN) levels (renal function test)
- You are pregnant or breastfeeding. Mesalamine is excreted in human breast milk. Discuss with your doctor.

WHILE using SALOFALK®:

- Discontinue use at first sign of rash or fever.

You may have your blood or urine tested regularly to monitor your kidney function since prolonged use of SALOFALK® may damage your kidneys.

Other warnings that you should know about:

Kidney stones may develop with use of mesalamine. 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 taking SALOFALK®. Talk to your doctor about how much water or other liquids you should be drinking.

INTERACTIONS WITH THIS MEDICATION

Interaction between azathioprine, 6-mercaptopurine, and aminosaliclylates (such as SALOFALK®) has been reported.

Drug interactions with coumarin, methotrexate, probenecid,

sulfapyrazone, spironolactone, furosemide, rifampicin, and Varicella Virus Vaccine (chicken pox vaccine) may be possible.

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.

PROPER USE OF THIS MEDICATION

Usual adult dose:

Acute episodes:

SALOFALK® rectal suspension, 4 g/60 g is self-administered on a daily basis during acute episodes of disease. Usually one unit-dose rectal suspension (4 g) is taken upon retiring (bedtime) and best results occur when retained in the rectum during the entire rest period. Discard unused portion.

Prevention or relapses:

SALOFALK® rectal suspension, 2 g/60 g is self-administered in the same manner as above on a daily basis to prevent relapse (recurrence of symptoms).

Continued use for a certain period may be recommended by your doctor to prevent symptoms from recurring. Check with your doctor should symptoms such as diarrhoea and rectal bleeding recur.

Overdose:

If you believe you have used too much, or in case of accidental oral ingestion, contact your doctor, 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 SALOFALK® doses at the same time to make up for a missed dose.

How to Use the Rectal Suspension:

Best results are achieved if the bowel is emptied immediately before the suspension is given.

1. Preparing the medication for administration:

- a) Shake the bottle well to make sure that the suspension is homogeneous.
- b) Remove the protective sheath from the applicator tip. Hold the bottle at the neck so as not to cause any of the medication to be discharged.

2. Assuming the correct body position:

- a) Best results are obtained by lying on the left side with left leg extended and the right leg flexed forward for balance, or the other way around if left-handed.

- b) An alternative to lying on the left side is the “knee-chest” position.

3. Administering the rectal suspension:

- a) Gently insert lubricated applicator tip into the rectum, pointed slightly toward the navel (umbilicus).
- b) Grasp the bottle firmly, then tilt slightly so that the nozzle is aimed toward the back, and squeeze slowly to instill the medication. Steady hand pressure will discharge most of the suspension. After administering withdraw and discard the used unit.
- c) Remain in position for at least 30 minutes to allow thorough distribution of the medication internally. Retain the suspension all night, if possible.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Rash, fever, and dizziness are common in patients allergic to sulfasalazine. Stop therapy at the first sign of a rash and contact your doctor.

Worsening of ulcerative colitis may occur and may include the following symptoms: abdominal or stomach cramps or pain (severe) and diarrhoea.

Other reported side effects reported with SALOFALK® suspension include abdominal pain or discomfort, abdominal cramps, abnormal coloration of the urine, constipation, cough, diarrhoea, dizziness, feeling of incomplete defecation, fever, flatulence, hair loss, headache, itching, lower back pain, rash and stools discoloured.

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Chest pain			✓
	Kidney stones (hard little pebbles that form in your kidneys); symptoms may include blood in urine, urinating more often and pain in your back, side, belly or groin.		✓	
Unknown	Pancreatitis (inflammation of the pancreas) with symptoms such as abdominal pain, nausea, vomiting, fever, rapid heartbeat, and feeling tired.			✓
	Allergic (hypersensitivity) reaction with symptoms such as rash, itching, fever, swelling of the mouth and throat, difficulty in breathing.			✓

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Myocarditis/ Pericarditis (inflammation of the heart muscle and lining around the heart) with symptoms such as pain in the chest, abnormal heartbeat, fatigue, fever, difficulty in breathing, accumulation of fluid in the lung, and coughing.			✓
Unknown	Liver problems with symptoms such as severe abdominal pain, nausea, vomiting, yellowing of the skin and eyes, drop in appetite, bloating and distension.		✓
	Acute intolerance syndrome with symptoms such as cramping, stomach pain, bloody and excessive stools, fever, headache and rash.		✓
	Interstitial pneumonia (lung abnormality with scarring) with symptoms such as difficulty in breathing, dry cough, fever, and persistent unwell feeling.		

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Aplastic anaemia (shortage of one or more types of blood cells) with symptoms such as 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.			✓

This is not a complete list of side effects. For any unexpected effects while taking SALOFALK®, contact your doctor or pharmacist.

HOW TO STORE IT

Store SALOFALK® rectal suspension at room temperature, preferably under 25°C. The expiration date and lot number are printed on the bottle.

Suspension colour may vary from off white to brown. Keep the medicine from light and air.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.allergan.ca or by contacting the sponsor, Aptalis Pharma Canada ULC at: 1-800-668-6424

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