PRODUCT MONOGRAPH

Pr**SALOFALK®**

Mesalamine Delayed Release Tablets USP,
500 mg

LOWER GASTROINTESTINAL TRACT ANTI-INFLAMMATORY

A07EC02

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Delayed release tablets 500 mg	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

SALOFALK® (mesalamine delayed release tablets) are indicated for adult patients for:
- treatment of acute ulcerative colitis
- prevention of relapse of Crohn's disease in patients following bowel resection

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

Pediatrics
Clinical studies with SALOFALK® tablets have not been performed in the pediatric population.

CONTRAINDICATIONS

SALOFALK® (mesalamine delayed release tablets) is contraindicated in:

- patients with severe renal impairment (GFR<30ml/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 unable to swallow the intact tablets.

Patients who are 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 delayed release tablets) 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 delayed release tablets) should only be used if the expected benefit clearly outweighs the risks to the patients.

SALOFALK® (mesalamine delayed release tablets) 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[1-3].

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 mesalamine[5].

Cases of pericarditis have also been reported as manifestation 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 sulfasalazine (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.

Patients with pyloric stenosis may have prolonged gastric retention of SALOFALK® tablets which could delay release of mesalamine in the colon.

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 delayed release tablets) 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 delayed release tablets) should be used only if the benefits outweigh the risks.

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 milk[9-12]. 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

Safety and effectiveness of SALOFALK® therapy in pediatric patients have not been established.

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 rash[16-19], pyrexia[16-19], 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[19,21], hepatitis[19], pericarditis, interstitial nephritis, interstitial pneumonia and pleural effusion. Interstitial pneumonia, pancreatitis and pericarditis have also been reported as manifestations of inflammatory bowel disease[22].

As with all 5-ASA products, exacerbations of ulcerative colitis characterized by cramping[18], acute abdominal pain[18,19,21] and diarrhoea[18-20] have been reported with mesalamine.

Other reported side effects include headache[18-20,23], flatulence[18], nausea[18-20,23], 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

Body System **Preferred term**	**SALOFALK®** **N=841** **%**	**Placebo** **N=176** **%**
Cardiac disorders		
Pericarditis	0.1	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
Proctalgia	1.1	0

Body System Preferred term	SALOFALK® N=841 %	Placebo N=176 %
Constipation	0.9	2.2
Anal discomfort	0.5	1.7
Pancreatitis	0.1	0
Condition aggravated	0.1	0
General disorders and administration site conditions		
Fatigue	3.3	4.5
Pyrexia	3	0
Administration site reactions	1.3	0.5
Edema 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
Spots	2.2	5.1
Pruritus	1.1	0.5
Alopecia	0.8	1.1

Post-Market Adverse Drug Reactions

Adverse Reactions Reported With the Use of SALOFALK® Tablets

The following adverse reactions have been identified during the post-approval use of SALOFALK® tablets. 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 discomfort, Abdominal pain (upper, lower), Diarrhoea, Faeces discoloured, Flatulence, Glossodynia, Nausea, Tongue discoloration, Tongue oedema

General Disorders And Administrative Site Disorders: Fatigue, Medication residue, Pyrexia **Investigations**: Sperm count decreased

Musculoskeletal And Connective Tissue Disorders: Back pain, Neck pain

Nervous System Disorders: Dizziness, Headache

Renal And Urinary Disorders: Chromaturia, Nephritis interstitial, Nephrolithiasis

Respiratory, Thoracic And Mediastinal Disorders: Lung infiltration, Interstitial pneumonia

Skin And Subcutaneous Tissue Disorders: Acute febrile neutrophilic dermatosis, Alopecia, Erythema, Pruritus, Rash, 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 aminosalicylates (including mesalamine) can increase the risk of leucopenia[1-3]. Other potential interactions with a number of drugs could occur (see Drug-Drug Interactions).

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[1-3].

Mesalamine could also increase renal and hematologic toxicity of methotrexate by additive effect and diminished absorption of folic acid[24].

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[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

In the acute ulcerative colitis inflammatory stage, and in the prevention of recurrence of Crohn's disease in adults, SALOFALK® (mesalamine delayed release tablets) must be taken reliably and consistently by the patient in order to ensure therapeutic success. Tablets should be swallowed whole before meals with plenty of fluid. Do not crush.

Recommended Dose and Dosage Adjustment

For the treatment of acute ulcerative colitis, two 500 mg SALOFALK® tablets, three or four times per day (total adult dose: 3 g/day – 4 g/day). Prolonged treatment may be required.

For the prevention of recurrence of Crohn's disease in patients following bowel resection, the total adult dose is 3 g/day in divided doses. Prolonged treatment is required.

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 take two SALOFALK® doses at the same time to make up for a missed dose.

Administration

Tablets should be taken consistently by the patient in order to ensure therapeutic success. Tablets should be swallowed whole before meals with liquid. Do not crush. Abrupt discontinuation is not recommended. Prolonged treatment may be required.

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.

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 cells[26].

The interference of mesalamine with either leukotriene or prostaglandin metabolism may play a major role in suppressing the inflammatory response mechanism[26-32]. 5-ASA prevents accumulation of thromboxane B2 and 6-keto-prostaglandin F1[27]. Both 5-ASA and SAS reverse H_2O, and Cl-secretion and increase Na+ secretion in experimentally-induced colitis in guinea pigs[33]. SAS and 5-ASA are known to inhibit polymorphonuclear cell migration possibly via lipoxygenase inhibition[32] 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[26].

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 generated[35]. 5-ASA acts as a dose dependent[35] 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 membrane[37]. 5-ASA also inhibits the formation of both eicosanoids and cytokines[29,36].

Pharmacodynamics

SALOFALK® tablets contains mesalamine (5-aminosalicylic acid, 5-ASA), the active principle of the prodrug sulfasalazine[38-40]. 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[27-32], interfere with leukotriene synthesis and consequent leukocyte migration[27,28] as well as act as a potent scavenger of free radicals[26]. Regardless of the mode of action, 5-ASA appears to be active mainly topically rather than systemically[41].

Pharmacokinetics

Absorption

Oral administration of mesalamine enteric-coated tablets allows passage through the stomach intact, despite an average gastric dwell time of close to 3 hours in non-fasting patients and delivery, at pH of 6.0, to sites of topical action in the lower gastrointestinal tract[27]. Disintegration of mesalamine enteric-coated tablets usually occurs in the terminal ileum and proximal colon, allowing patients with ileal involvement to benefit from the drug. At the same time, most side effects attributed to the sulfapyridine moiety of SAS are avoided.

In a cross-over study to determine gastrointestinal transit and disintegration characteristics in the fed and fasted state in healthy subjects (n=8), gastric emptying of mesalamine enteric-coated tablets was delayed by the presence of food. The tablets tended to disintegrate about five hours after leaving the stomach. Although the time between dosing and tablet disintegration was longer in fed subjects, there was no significant difference in disintegration times between the fasted and fed subjects once the tablet left the stomach. The enteric coating appeared to be unaffected by gastric retention time. Site of disintegration was affected by the rate of intestinal transit. In three of four subjects showing the slowest intestinal transit, disintegration occurred in the ileum. In eight instances (50%; 5 fed/3 fasted subjects), disintegration occurred in the ascending colon. In three instances, disintegration occurred beyond the ascending colon (1 fed/2 fasted). In the remaining two instances, the precise point of disintegration could not be accurately determined.[42]

In a study of 13 patients with inflammatory bowel disease six with ulcerative colitis, one with total colectomy, seven with Crohn's disease, two with right hemi-colectomy), the tablets disintegrated with a mean time of 3.2 hours after leaving the stomach. For nine of the 11 patients for whom disintegration time could be accurately determined, this occurred within one hour of the mean time. Overall, tablet disintegration occurred in the small intestine in over 60% of the patients. Subsequently, the tablet became finally dispersed and remained in the colon for many hours[43].

Bioavailability has further been confirmed by measurement of 5-aminosalicylic acid in the ileostomy effluent of patients with or without small bowel resection receiving mesalamine enteric-coated tablets. Approximately 53% of mesalamine thus administered could be recovered in the effluent.

Pharmacokinetic data suggest that oral 5-ASA (mesalamine) is partially absorbed, excreted rapidly (range $t_{1/2}$ = 0.4-2.4 hours[41,44]), and partially recovered unchanged in the faeces[49].

Distribution

In patients with active ulcerative colitis of Crohn’s disease receiving 500 mg of oral 5-ASA t.i.d., mean steady state plasma levels of 5-ASA and N-acetyl-5-ASA averaged 0.7 and 1.2

µg/mL respectively and were reached within 4-6 hours after administration. Treatment with a smaller dose (250 mg t.i.d.) achieved levels of 0.4 and 1.0 µg/mL, respectively.[41,49]

Metabolism
5-ASA is metabolized 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]. The site of metabolism has not been elucidated. 5-ASA and its major metabolite N-acetyl-5-aminosalicylic acid are short lived in serum being excreted rapidly. N-acetyl-5-ASA exhibits a half life-reported at 5-10 hours[41]. The elimination half life of 5-ASA appears to be dose dependent (1.4 ± 0.6 hours at 500 mg t.i.d. vs. 0.6 ± 0.2 hours at 250 mg t.i.d. [41,44]).

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. Urinary clearance of absorbed drug occurs rapidly, mainly as the acetylated metabolite. The mean recovery rate in urine following oral administration of 5-ASA has been estimated at approximately 44%. A fecal recovery rate of 35% consisted of both unabsorbed drug and the acetylated metabolite.[41,44]

STORAGE AND STABILITY
SALOFALK® (mesalamine delayed release tablets) should be stored at controlled room temperature (15°-30°C). Protect from exposure to light.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Each ochre colored, oblong, biconvex SALOFALK® tablet contains: mesalamine 500 mg.

Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, glycine, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polydimethyl siloxane, polysorbate, povidone, sodium carbonate, sodium hydroxide, talc, titanium dioxide, triethyl citrate. SALOFALK® (mesalamine delayed release tablets) are gluten-free and phthalate-free.

SALOFALK® tablets are supplied in bottles of 150 and 500 tablets.

PART II: SCIENTIFIC INFORMATION

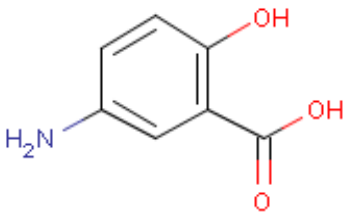
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: 5-aminosalicylic acid, mesalamine

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

Molecular formula and molecular mass: $C_7H_7NO_3$ 153.14



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

Ulcerative Colitis

A placebo-controlled, parallel group, multicentre study was conducted in 136 out-patients with ulcerative colitis. Patients were administered SALOFALK® tablets at doses of 4 g/day (n=47) and 2 g/day (n=45), or placebo (n=44) for 6 weeks. At Week 3, patients in the 4 g mesalamine group were rated less severe than placebo patients for rectal bleeding, mucosal appearance and physician's overall rating of disease severity ($p<0.05$). Although there was improvement for patients in the 2 g mesalamine group relative to placebo, differences

between the two groups were not statistically significant. Similar differences between the two groups were seen at Week 6.[45]

In an 8 week randomized, double-blind, parallel group study mesalamine tablets (1.5 g/day) were compared to sulfasalazine (3.0 g/day) in patients with mild to moderate ulcerative colitis. Of the 164 patients eligible for efficacy analysis, 87 received mesalamine and 77 sulfasalazine. After 4 weeks, 71% and 66% of patients taking mesalamine and sulfasalazine, respectively, had achieved remission (p=0.338). At 8 weeks, 74% and 81% achieved remission, respectively (p=0.835). Endoscopic remission at 8 weeks was recorded in 49% of patients taking mesalamine and 47% taking sulfasalazine (p=0.272).[19]

Crohn's Disease

Recurrence of Crohn's disease after surgical resection was investigated in a randomized, controlled study in which patients received 1.5 g mesalamine tablets twice a day or placebo, within 8 weeks following surgery, for up to 72 months. At yearly intervals, patients were assessed. Symptomatic recurrence was defined as having symptoms judged to be caused by Crohn's disease that required treatment plus radiological or endoscopic evidence of disease. The symptomatic recurrence rate in the treatment group was 31% (27 of 87) compared with 41% (31 of 76) in the control group (p=0.031). Using an intent-to-treat analysis, the relative risk of developing recurrent disease was 0.628 (90% CI, 0.40-0.97) for patients in the treatment group (p=0.039; one-tail test) and 0.532 (90% CI, 0.32-0.87) using an efficacy analysis. The endoscopic and radiological rate of recurrence was also significantly decreased with a risk of 0.635 (90%, CI 0.44-0.91) for the efficacy analysis.[46]

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 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 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 and above[47].

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[4].

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. 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[48-50].

Diener *et al.* [51] 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.

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PART III: CONSUMER INFORMATION

[Pr]SALOFALK®
Mesalamine Delayed Release Tablets USP, 500 mg

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® tablets are used for the treatment of acute ulcerative colitis (inflammation of the lining of the large bowel and rectum) and in the prevention of relapse of Crohn's disease in patients following bowel resection.

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/1.73m^2) and/or severe liver (hepatic) impairment (see WARNINGS AND PRECAUTIONS)
- You are allergic to this drug or to any ingredient in the formulation (see **What the non-medicinal ingredients are)**
- You have stomach or small intestinal ulcers
- You have urinary tract obstructions
- You have a sensitivity to salicylates, for example acetylsalicylic acid (Aspirin®)
- You are unable to swallow the intact tablet
- The patient is an infant under two years of age

What the medicinal ingredient is:
SALOFALK® tablets contain 500 mg mesalamine (me-SAL-a-meen), also known as 5-aminosalicylic acid, 5-ASA or mesalazine.

What the non-medicinal ingredients are:
SALOFALK® tablets contains carnauba wax, colloidal silicon dioxide, glycine, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polydimethyl siloxane, polysorbate, povidone, sodium carbonate, sodium hydroxide, talc, titanium dioxide, triethyl citrate. SALOFALK® tablets are gluten-free and phthalate-free.

What dosage forms it comes in:
SALOFALK® 500 mg tablet is available for oral administration as an ochre-coloured (pale yellow), oblong, enteric-coated tablet.

SALOFALK® 500 mg tablet is supplied in bottles of 150 and 500.

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 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), or salicylates (Aspirin®)
- 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 have pyloric stenosis (a narrowing of the outlet from the stomach that causes contents of the stomach to remain there for a longer period of time). Pyloric stenosis may keep the SALOFALK® tablet from reaching the colon as quickly as it normally would
- 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.

INTERACTIONS WITH THIS MEDICATION

Interaction between azathioprine, 6-mercaptopurine 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.

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:
For the treatment of acute ulcerative colitis: Two 500 mg SALOFALK® tablets, three or four times daily.

For the prevention of recurrence of Crohn's disease in patients following bowel resection: 3 g/day in divided doses.

Tablets should be taken consistently for treatment success. Tablets should be swallowed whole before meals with liquid. Do not crush the tablets. Abrupt discontinuation is not recommended.

Overdose:

If you believe you have taken too many tablets, 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®, take your dose as soon as possible, unless it is almost time for the next dose. Do not take two SALOFALK® doses at the same time to make up for a missed dose.

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® tablets include abdominal pain or discomfort, abnormal coloration of the urine, back and neck pain, cough, diarrhoea, dizziness, flatulence, fever, burning or tingling sensation in the mouth, hair loss, headache, itching, inflammation of heart muscle, nausea, kidney stones, rash, stools discoloured, tiredness, tongue discoloration and tongue swelling.

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			✓
Unknown	Pancreatis (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, and difficulty in breathing..			✓
	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.			✓
	Liver problems with symptoms such as severe abdominal pain, nausea, vomiting, yellowing of the skin and eyes, drop in appetite, bloating and distension.			✓

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**	
Unknown	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.			✓
	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

SALOFALK® tablets should be stored at controlled room temperature (15°-30°C). Protect from exposure to light. 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:
http://www.aptalispharma.com
or by contacting the sponsor, Aptalis Pharma Canada Inc., at:
1-800-565-3255

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