PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSULCRATE®

Sucralfate

Tablets, 1 g, Oral use

USP standard

PrSULCRATE® SUSPENSION PLUS

Sucralfate

Oral Suspension, 1 g/5 mL, Oral use

Gastro-Duodenal Cytoprotective Agent

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St-Laurent, Quebec
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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SULCRATE (sucralfate) Tablets is indicated for:

- the treatment of duodenal and non-malignant gastric ulcer.
- for the prophylaxis of duodenal ulcer recurrence

SULCRATE SUSPENSION PLUS is indicated for:

- the treatment of duodenal ulcer and for the prophylaxis of gastrointestinal hemorrhage due to stress ulceration in critically ill patients.

1.1 Pediatrics (< 18 years of age)

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

1.2 Geriatrics (>65 years of age)

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

2 CONTRAINDICATIONS

Sucralfate is contraindicated in:

- Patients who are hypersensitive to sucralfate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use caution when prescribing/administering this drug in pregnant or pediatric patients, or patients of childbearing potential (see 7 WARNINGS AND PRECAUTIONS).

- Tablets

In the case of gastric ulcers, an alternative treatment should be considered if no objective improvement is observed following 6 weeks of SULCRATE therapy. However, patients with a large gastric ulcer that has demonstrated a progressive healing tendency may require an additional 6 weeks of treatment.

- Suspension

SULCRATE suspension must not be administered intravenously.

Duration of continuous treatment in patients with chronic renal failure receiving dialysis should be evaluated by periodic monitoring of serum aluminum levels, due to the possibility of aluminum accumulation in these patients (see 7 WARNINGS AND PRECAUTIONS). According to information widely available in the literature, patients with serum aluminum concentrations that approach 100

mcg/L should be carefully monitored for symptoms of aluminum toxicity and treatment should be discontinued if such symptoms appear.

There is no evidence to indicate that patients with chronic renal failure, who do not require dialysis, are at risk of developing aluminum toxicity while receiving the recommended doses of sucralfate. Healthcare professional discretion should be exercised when considering the duration of treatment (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

- **Duodenal ulcer**

Tablets:

The recommended adult oral dosage one tablet of 1 g four times a day.

In duodenal ulcers, while healing with SULCRATE often occurs within two to four weeks, treatment should be continued for a maximum of 8 to 12 weeks unless healing has been demonstrated by X-Ray and/or endoscopic examination.

Suspension:

The recommended adult dose of SULCRATE SUSPENSION PLUS for the treatment of (acute) duodenal ulcer is 2 g (10 mL) twice a day.

- **Non-malignant gastric ulcer**

The recommended adult oral dosage is one tablet of 1 g four times a day.

- **Prophylaxis of duodenal ulcer recurrence**

Tablets:

For the prophylaxis of duodenal ulcer recurrence, the recommended dosage is one tablet of 1 g twice daily, on an empty stomach. Treatment may be continued for up to one year. For relief of pain, antacids may be added to the treatment. However, antacids should not be taken within ½ half hour before or after SULCRATE intake.

- **Prophylaxis of gastrointestinal hemorrhage due to stress ulceration**

Suspension:

For the prophylaxis of gastrointestinal hemorrhage due to stress ulceration, administer 1 g (5 mL) orally or via nasogastric tube four to six times a day. To prevent clogging of the nasogastric tube flush with 10 mL of water following each administration.

The duration of treatment for prophylaxis of stress ulceration must be individually determined. Treatment should be continued for as long as one or more of the risk factors for stress ulceration is present but normally not for more than 14 days.

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

4.4 Administration

- **Duodenal ulcer**

Tablets:

The SULCRATE tablets are administered four times a day, one hour before meals and at bedtime, on an empty stomach. For duodenal ulcer, SULCRATE may also be administered as two 1 g tablets twice daily, on waking and at bedtime on an empty stomach.

Suspension:

SULCRATE SUSPENSION PLUS (10 mL) is administered twice a day on waking and at bedtime on an empty stomach.

- **Non-malignant gastric ulcer**

Tablets: The SULCRATE tablets are administered four times a day, one hour before meals and at bedtime, on an empty stomach.

- **Prophylaxis of duodenal ulcer recurrence**

Tablets: For the prophylaxis of duodenal ulcer recurrence, the tablets must be administered on an empty stomach. If antacids are added to the treatment, the antacids should not be taken within half hour before or after SULCRATE intake.

- **Prophylaxis of gastrointestinal hemorrhage due to stress ulceration**

Suspension: Administer 1 g (5 mL) orally or via nasogastric tube. To prevent clogging of the nasogastric tube flush with 10 mL of water following each administration.

4.5 Missed Dose

In the event that a dose is missed, the patient should take the missed dose as soon as they remember. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the regular time. The patient should not take two doses at the same time.

5 OVERDOSAGE

Overdosage has never been observed with SULCRATE and appears to be unlikely since, using maximal doses of up to 12 g/kg/body weight in a variety of animal species, a lethal dose could not be established.

Overdosage is likely to be associated with symptoms similar to those described in the 8 ADVERSE REACTIONS section, such as constipation. These should be treated symptomatically.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral use	Tablet / 1 g	Calcium carboxy-methylcellulose, hydrogenated vegetable oil, magnesium stearate and microcrystalline cellulose
Oral use	Oral Suspension 1 g/5 mL	Butterscotch flavour, glycerine, sodium methylparaben, sodium phosphate monobasic, sodium propylparaben and xanthan gum

Tablets:

Each white, capsule-shaped, biconvex tablet, embossed with "SULCRATE" on one side and debossed with "HMR" on the other side, contains 1 g of sucralfate. Available in bottles of 100 tablets.

Suspension:

Each 5 mL of off-white, creamy, suspension with a caramel odour contains 1 g of sucralfate. Available in bottles of 500 mL.

7 WARNINGS AND PRECAUTIONS

General

SULCRATE must not be administered intravenously. Inadvertent intravenous administration of insoluble sucralfate and its insoluble excipients may induce fatal complications including pulmonary and cerebral emboli. Other severe complications including aluminum intoxication are reported after intravenous administration.

The following should be taken into account before treating patients with SULCRATE (sucralfate):

- Recurrence may be observed in patients after a successful course of treatment for gastric or duodenal ulcers. While the treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the underlying cause of ulcer disease.
- Proper diagnosis is important since symptomatic response to sucralfate therapy does not rule out the presence of a gastric malignancy.
- Isolated reports of sucralfate tablet aspiration with accompanying respiratory complications have been received. Therefore, sucralfate tablets should be used with caution by patients who have known conditions that may impair swallowing, such as recent or prolonged intubation, tracheostomy, prior history of aspiration, dysphagia, or any other conditions that may alter gag and cough reflexes, or diminish oropharyngeal coordination or motility.
- Due to the carbohydrate content of sucralfate suspension excipients, episodes of hyperglycemia have been reported in diabetic patients. Close monitoring of glycemia in diabetic patients treated

with sucralfate suspension is recommended. Adjustment of the anti-diabetic treatment dose during the use of sucralfate suspension might be necessary.

Renal

Chronic Renal Failure

- Dialyzed Patients

Sucralfate should be used with caution in patients with chronic renal failure. When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract (see 10 CLINICAL PHARMACOLOGY, Chronic Renal Failure and Dialysis Patients). Existing evidence indicates that patients with normal renal function receiving the recommended doses of sucralfate adequately excrete aluminum in the urine; however, patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum, and in these individuals, aluminum is known to accumulate in serum and in tissues. In particular, dialysis patients are at greater risk as aluminum does not cross dialysis membranes of the dialysis machine since it is bound to plasma proteins, most notably albumin and transferrin.

In patients with chronic renal failure undergoing dialysis, aluminum-related toxicity (encephalopathy and aluminum-related bone disease), associated with the administration of sucralfate and/or other sources of aluminum has been reported. Consideration should therefore be given to the total daily load of aluminum before administering sucralfate in combination with other aluminum-containing medications, such as aluminum-containing antacids.

- Nondialyzed Patients

In a study of six nondialyzed chronic renal failure patients with glomerular filtration rates ranging from approximately 10 to 40% of normal, sucralfate administered at a dose of 1 g QID for three weeks resulted in elevated serum aluminum concentrations which plateaued at approximately 23 mcg/L after one week of treatment from a pretreatment level of 3 mcg/L. Renal aluminum clearance increased in relation to the increase in serum levels and returned to baseline within two weeks following discontinuation of sucralfate as did serum aluminum concentrations. No adverse events were reported in these patients.

These data indicate that the use of sucralfate in nondialyzed chronic renal failure patients requires healthcare professional discretion since the excretion of absorbed aluminum may be impaired in these individuals.

7.1 Special Populations

7.1.1 Pregnant Women

Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.1.2 Breast-feeding

It is unknown if SULCRATE tablets or SULCRATE SUSPENSION PLUS is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Cases of hypersensitivity have been reported with the use of sucralfate, including anaphylactic reactions, bronchospasm, dyspnoea, laryngeal oedema, lip swelling, oedema mouth, pharyngeal oedema, pruritus, rash, respiratory tract oedema, swelling face and urticaria.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

- SULCRATE Tablets

Very few side effects have been reported with SULCRATE tablets. They are mild in nature and have only exceptionally led to discontinuation of therapy.

The main complaint has been constipation ranging from 1.7% to 3.3% of patients.

Other side effects reported included diarrhea, nausea, gastric discomfort, indigestion, dry mouth, back pain, dizziness, sleepiness and vertigo.

- SULCRATE SUSPENSION PLUS

In a placebo-controlled clinical trial involving 184 patients, the adverse event rates for SULCRATE SUSPENSION PLUS were similar to that seen in the placebo group (SULCRATE SUSPENSION PLUS 10.2% vs placebo 7.4%). The most common adverse event was headache (3.4%) followed by nausea (2.3%), abdominal pain (2.3%), constipation (1.1%), diarrhea (1.1%), and urticaria (1.1%). Only headache, abdominal pain and nausea had a higher incidence in the SULCRATE SUSPENSION PLUS group relative to placebo.

See section 7 WARNINGS AND PRECAUTIONS, Dialyzed Patients for information on the potential for aluminum toxicity in dialyzed chronic renal failure patients.

Due to the carbohydrate content of sucralfate suspension excipients, episodes of hyperglycemia have been reported in diabetic patients.

8.3 Less Common Clinical Trial Adverse Reactions

Not available.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Not Available.

8.5 Post-Market Adverse Reactions

The following adverse reaction has been identified during post approval use of SULCRATE.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Post-marketing cases of hypersensitivity have been reported with the use of sucralfate, including anaphylactic reactions, bronchospasm, dyspnoea, laryngeal oedema, lip swelling, oedema mouth, pharyngeal oedema, pruritus, rash, respiratory tract oedema, swelling face and urticaria.

Bezoars have been reported in patients treated with sucralfate (SULCRATE® tablets and SULCRATE® SUSPENSION PLUS). The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

In patients with chronic renal failure undergoing dialysis, aluminum-related toxicity (encephalopathy and aluminum-related bone disease), associated with the administration of sucralfate and/or other sources of aluminum has been reported.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Potential interactions with a number of drugs could occur. See 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

- The healthcare professional should consider the possible clinical implications of these interactions. It is recommended to separate the administration of any drug from that of sucralfate when the potential for altered bioavailability is felt to be critical to the effectiveness of that drug.
- Unless specified, the above data are based on studies carried out with SULCRATE tablets.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antacids	C, As	Decreased binding of sucralfate with the gastro-duodenal mucosa	Antacids should not be taken within half an hour before or after sucralfate intake because of the possibility of decreased binding of sucralfate with the gastro-duodenal mucosa as a consequence of a change of intra-gastric pH
Tetracycline, phenytoin, or cimetidine	AS	Reduction in the bioavailability of tetracycline, phenytoin or cimetidine	Animal studies have shown that simultaneous administration of sucralfate with tetracycline, phenytoin or cimetidine results in a statistically significant reduction in the bioavailability of these agents. Cimetidine absorption was not reduced in humans
Digoxin	CT	Reduction in the bioavailability of digoxin	Concomitant administration of sucralfate reduced the bioavailability of digoxin. Complete bioavailability was restored by separating the administration of sucralfate from that of the other agent by 2 hours
Phenytoin, warfarin, or fluoroquinolone antibiotics	CT	Reduction in the bioavailability of phenytoin, warfarin, or fluoroquinolone antibiotics	Simultaneous administration of sucralfate with phenytoin, warfarin, and fluoroquinolone antibiotics results in reduced absorption of these agents. Complete bioavailability was restored by separating the administration of sucralfate from that of the other agent by 2 hours
ASA or ibuprofen	C	Bioavailability unaltered	Administration of sucralfate 30 and 60 minutes before ASA or ibuprofen did not alter the bioavailability of these agents, respectively

Proper/Common name	Source of Evidence	Effect	Clinical comment
Naproxen, indomethacin, or ketoprofen	C	Reduced peak concentration, delay in time to peak concentration	Prior administration of a single dose of sucralfate tablets reduced peak concentration and delayed time to reach peak concentration with naproxen, indomethacin, or ketoprofen
Naproxen	C	Reduced peak concentration, delay in time to peak concentration	SULCRATE SUSPENSION PLUS administration one-half hour before naproxen administration reduced peak concentration and delayed time to reach peak concentration with naproxen

Legend: C = Case Study; CT = Clinical Trial; AS= Animal Studies; T = Theoretical

Sucralfate, administered respectively 30 and 60 minutes before ASA or ibuprofen did not alter the bioavailability of these agents.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

Sulfated polysaccharide has been known for a long time to possess an inhibitory action on proteolytic activity of pepsin and a preventive action on experimental peptic ulcerations.

Sucralfate, a disaccharide sulfate, has been shown to have a strong antipepsin and antiulcer action.

Contrary to the more polymerized saccharides, sucralfate is devoid of any anti-coagulant activity.

Moreover, it has been found that enhanced antiulcerogenic activity was more pronounced with the aluminum salt of the disaccharide, sucralfate.

In vitro and clinical studies have shown that sucralfate is not an antacid. Sucralfate has no effect on the cardiovascular system or central nervous system and on the hematopoietic system including blood coagulation factors.

10.1 Mechanism of Action

SULCRATE (sucralfate) exerts a generalized gastric cytoprotective effect by enhancing natural mucosal defense mechanisms. Studies conducted in animals and clinical trials in humans have demonstrated that sucralfate can protect the gastric mucosa against various irritants such as alcohol, acetylsalicylic acid (ASA), hydrochloric acid, sodium hydroxide or sodium taurocholate.

In addition, sucralfate has been demonstrated to have a greater affinity for ulcerated gastric or duodenal mucosa than for non-ulcerated mucosa.

Sucralfate produces an adherent and cytoprotective barrier at the ulcer site. This barrier protects the ulcer site from the potential ulcerogenic properties of acid, pepsin and bile.

Furthermore, sucralfate blocks acid diffusion across the sucralfate protein barrier and also complexes directly with pepsin and bile.

10.2 Pharmacodynamics

Sucralfate produces distinct morphologic and functional changes in the normal gastric mucosa: mucus release, changes in ion transport and increased release of luminal prostaglandins. Several studies have shown that it can increase the synthesis and release of prostaglandin E2 from the mucosa. This mechanism may in part explain its effective cytoprotective properties.

Results of in vivo and in vitro studies show that sucralfate produced an adherent and cytoprotective barrier at the ulcer site which resisted degradation by acid and pepsin.

Laboratory and clinical studies indicate that sucralfate promotes the healing of gastric and duodenal ulcers by a three-way action:

- Formation of a chemical complex that binds to the ulcer site to establish a protective barrier.
- Direct inhibition of the action of pepsin and bile.
- Blockage of the back diffusion of gastric acid across the barrier.

The binding of sucralfate was demonstrated in rats with experimentally-induced ulcers. After a single dose of sucralfate, the ulcerated organs were excised and washed with a fluorescent compound that was taken up by sucralfate. Under ultraviolet light, the sucralfate showed affinity for the areas of ulceration, substantiating the binding action.

The affinity of sucralfate for the ulcer site was further substantiated in a study where patients were scheduled for gastric resection. Each patient received the same daily dose of sucralfate, with the interval from the last dose to operation time varying from 2 to 16 hours. At all of these intervals, the concentrations of sucralfate in ulcer craters were 4 to 30 times higher than the concentrations in tissue specimens from the normal mucosa in the same patients.

The antipepsin activity of sucralfate has been demonstrated in several in vivo and in vitro studies.

In in vitro studies and on pylorus ligated rat models, the presence of sucralfate inhibits pepsin activity of the gastric juice, reduces the total acidity and is associated with an elevation of gastric fluid pH.

In a clinical study, sucralfate was administered to ulcer patients and the effects on pepsin activity was monitored for 30 minutes after ingestion of the drug. Sucralfate doses of 1, 1.5, 2, 2.5 and 3 g reduced pepsin activity by 32%, 34%, 44% and 55% respectively.

Sucralfate was shown to reduce bile salt concentration in vitro by adsorbing the bile salts onto sucralfate in suspension. Glycocholic acid in a buffered solution was used in the test. The maximum amount adsorbed was approximately 112 mg per gram of sucralfate.

Sucralfate's capacity to block the diffusion of acid was demonstrated in an in vitro diffusion cell experiment. Sucralfate was bonded to an albumin film and placed between two solutions of equal acidity. When the acidity on the sucralfate side of the film was increased, a lowering of pH on the other side was delayed. Sucralfate delayed the change more than twice as long as albumin alone and nearly twice as long as albumin plus an antacid.

The capacity of sucralfate to block acid diffusion was further substantiated in a clinical study. Gastric transmural potential difference was measured in normal volunteers after the administration of either glycocholic acid or sucralfate followed with glycocholic acid. The drop in potential difference produced by the administration of glycocholic acid was reduced when sucralfate was administered before glycocholic acid, indicating a reduction in the back diffusion of acid.

During therapy, the physiological functions of the digestive system remain virtually unchanged.

10.3 Pharmacokinetics

Absorption

The action of sucralfate is non-systemic as the drug is only minimally absorbed from the gastrointestinal tract. The minute amounts of the sulfated disaccharide which are absorbed are primarily excreted in the urine.

Each gram of sucralfate contains approximately 200 mg of aluminum. The aluminum moiety can dissociate at low pH and aluminum release in the stomach can be expected; however, aluminum is poorly absorbed from the intact gastrointestinal tract. Following administration of 1 g of sucralfate (tablets or suspension) four times a day to individuals with normal renal function, approximately 0.001% to 0.017% of sucralfate's aluminum content is absorbed and excreted in the urine. This results in an aluminum load of between 0.008 mg and 0.136 mg following a 4 g daily dose. Individuals with normal renal function excrete absorbed aluminum and can respond to an increased aluminum load by increasing urinary excretion.

These values were determined in individuals with intact gastrointestinal mucosa. Available evidence does not indicate that absorption of aluminum would be different in individuals with ulcerated gastrointestinal mucosa.

Experiments have shown that sucralfate is not an antacid.

Special Populations and Conditions

- Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been

described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure. See section 7 WARNINGS AND PRECAUTIONS, Renal.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 and 30°C.

Protect SULCRATE SUSPENSION PLUS from freezing.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

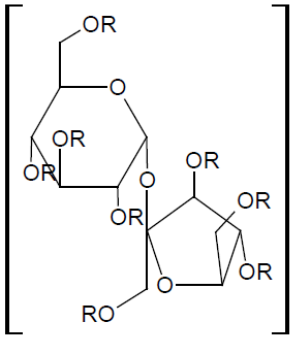
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	sucralfate
Chemical name:	3,4,5,6-Tetra-(polyhydroxyaluminum)-alpha-D-glucopyranosylsulfate-2,3,4,5,-tetra-(polyhydroxyaluminum)-beta-D-fructofuranoside sulfate
Molecular formula and	$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]x[H_2O]y$ X = 8 to 10; y = 22 to 31
molecular mass:	2483 to 2801

Structural formula:



$[Al(OH)_3]$ x $[H_2O]y$

(x=8 to 10 and y= 22 to 31)

R= $SO_3Al(OH)_2$

Physicochemical properties:

- Sucralfate occurs as a white to slightly yellowish white, amorphous powder.
- Sucralfate is an aluminum salt of a sulfated disaccharide.
- It is soluble in dilute hydrochloric acid and sodium hydroxide but practically insoluble in water, boiling water, ethanol or chloroform.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Duodenal Ulcer

Trial Design and Study Demographics

The safety and efficacy of SULCRATE in duodenal ulcer has been demonstrated in a number of controlled as well as non-controlled studies involving more than 1000 patients. The drug was compared under double-blind conditions to a placebo or cimetidine. Diagnosis and clinical findings were controlled with endoscopic examinations. The average daily dosage utilized was 3 to 4 g a day and the duration of treatment varied between 4 to 12 weeks.

Study Results

Complete healing of duodenal ulcers was observed in 83.9% of patients treated with SULCRATE® tablets compared to 57.2% of patients treated with a placebo.

When SULCRATE® suspension was compared to placebo the healing rate observed after 8 weeks treatment was 76% of patients treated with SULCRATE® suspension and 53% of patients given placebo. In another study the healing rates of SULCRATE® suspension and SULCRATE® tablets administered as 1 g qid for 8 weeks, were similar: 84% vs 85% respectively.

In an eight-week double-blind study of SULCRATE® SUSPENSION PLUS administered as 2 g BID versus placebo suspension and involving 184 patients, the healing rate after 8 weeks of treatment for patients treated with SULCRATE® SUSPENSION PLUS was 74% versus 55% for placebo.

In two comparative studies of SULCRATE® tablets and cimetidine, there was no statistical difference in healing rates between the two drugs.

Duodenal Ulcer Recurrence

Trial Design and Study Demographics

Over 300 patients have participated in controlled clinical trials evaluating the efficacy of SULCRATE tablets in preventing duodenal ulcer recurrence. A multicenter, double-blind, placebo-controlled study conducted in the US resulted in a significantly lower incidence of duodenal ulcer recurrence in patients treated with SULCRATE tablets for up to one year.

Study Results

Table 3 - Primary Efficacy Analysis for clinical trials in Duodenal Ulcer Recurrence

Treatment group	**Primary Efficacy endpoint: Incidences of recurrence by endoscopic evaluations**	
	Study Results	
	6 months	**12 months**
SULCRATE Tablets	20 %	27 %
Placebo	74 %	80 %

In the course of the trial, some investigators have noted symptoms that could be suggestive of duodenal ulcer in some patients receiving prophylaxis with SULCRATE tablets. However, these symptoms did not result in duodenal ulcer disease.

Gastric Ulcer

Trial Design and Study Demographics

The effect of SULCRATE® tablets in gastric ulcer was evaluated under double-blind conditions in approximately 450 patients.

Study Results:

The healing rate for patients receiving SULCRATE tablets was 74.1% as compared to 53.1% in patients receiving a placebo.

In a comparative study of SULCRATE and cimetidine in 41 patients, the healing rate was comparable in both groups of patients.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

LD_{50} acute toxicity studies were completed in various rodent species and LD_{50} could not be determined. Doses utilized in these studies were as high as 12 g/kg of body weight orally in the rat and 8 g/kg of body weight administered intraperitoneally in the mouse. Dogs received sucralfate at doses up to 5 g/kg. No drug-related toxicity or deaths were observed.

Subacute Toxicity

Two subacute toxicity studies were conducted in the rabbit and guinea pig to determine the effect of sucralfate on the cecum and large bowel. Doses up to 1000 mg/kg/day for 30 days were used and detailed gross and histopathological examinations of the entire digestive tract were accomplished at the termination of the study. The results indicated that the administration of sucralfate under the conditions of these studies did not have any adverse effect on any area of the digestive tract or in any other organ system.

In addition, no effect was seen in terms of the hematological or blood chemical parameters examined in the guinea pig study. In this study, blood was also analyzed for aluminum content and no increases in blood aluminum levels were seen when test groups were compared with controls.

In a 30-day subacute study, sucralfate was given to groups of rats at doses of 2, 4 and 8 g/kg/day. No toxicity was evidenced in terms of general condition, behavior, hematology, blood chemistry or organ weights. The high dose rats did exhibit some weight gain depression. Histological examination of tissues revealed some neutrophil infiltration in the submucosa and the tunica propria mucosae of the stomach in 6 of 20 animals of the 8 g/kg/day group. A similar finding was seen in 3 rats receiving 4 g/kg/day but it was lesser in degree. No other findings were noted. The no-effect level was 2 g/kg/day.

Carcinogenicity:

The effect of prolonged administration of sucralfate was examined in mice, rats and dogs. Sucralfate was given to mice at doses of 1 and 5% of the diet in both a one-year chronic toxicity study and a two-year carcinogenicity study. No untoward deleterious effects were reported in either study and no evidence of carcinogenic potential was manifested. A second 109-week carcinogenic study was conducted in mice using doses up to 1000 mg/kg/day. This study confirmed those findings reported in the two earlier studies.

In a six-month rat chronic study, sucralfate was given at doses of 0.5, 1, 2, and 4 g/kg/day by oral gavage. No evidence of toxicity was noted in appearance, hematology, blood chemistry or organ weights.

The stomachs of animals in the 2 and 4 g/kg/day groups that were sacrificed after 90 days exhibited some neutrophilic infiltration of the submucosa and the tunica propria with concurrent hydropic degeneration or slight thickening of the mucosal epithelium. These responses were more advanced after six months. Degenerative changes were also seen in the epithelial cells of the renal tubules at 4 g/kg/day and to a lesser extent at 2 g/kg/day. The no-effect levels were in between 1 and 2 g/kg/day. These doses are in excess of 15 times that recommended for humans.

A twenty-four month chronic toxicity/carcinogenicity study was also conducted in rats. Eosinophilic cytoplasmic droplets were seen in renal tubule epithelial cells in rats of the 1000 and 250 mg/kg/day groups. Untreated control animals and those receiving 50 mg/kg/day did not have this renal finding. Behavioral observations, blood chemistry assays and urinalysis tests were comparable among all groups indicating normal kidney function. Therefore, the renal findings were not considered clinically meaningful. In addition, the findings of the microscopic examination of all other tissues were similar among the groups. Finally, no carcinogenic potential was apparent.

Dogs received sucralfate at doses up to 2 g/kg/day for six months. No untoward drug-related effects were reported. Similar results were obtained in a one-year dog study where the dogs received 50, 250 and 500 mg/kg/day sucralfate.

However, microscopic examination together with subsequent electron microscopic analysis disclosed a vacuolation of some of the epithelial cells in the proximal convoluted tubules in some of the 250 and 500 mg/kg/day animals. No morphological alterations were seen with other compounds such as mannitol, dextran, sucrose or polyvinylpyrrolidone.

The changes were non-progressive since they may be seen after 4 weeks and they are reversible. In addition, none of the blood chemistry or kidney function tests conducted indicated renal damage nor was the normal function of the kidneys hindered.

It is noted that no drug-associated cellular changes in renal tissues were cited in the 28-day guinea pig, 30-day rabbit or 109-week mouse studies discussed previously.

Reproductive and Developmental Toxicology:

Reproduction and teratological studies with sucralfate doses up to 4 g/kg/day body weight in mice and rats and up to 1000 mg/kg of body weight in rabbits did not demonstrate any teratogenic or other associated abnormalities. No deleterious drug-associated effects were seen in terms of general reproductive performance, fertility or perinatal/post-natal responses. The drug levels employed represented doses ranging from 15 to 45 times those recommended in humans.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SULCRATE / SULCRATE SUSPENSION PLUS

Sucralfate tablets USP / Sucralfate oral suspension

Read this carefully before you start taking **SULCRATE / SULCRATE SUSPENSION PLUS** 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 **SULCRATE / SULCRATE SUSPENSION PLUS**.

What is SULCRATE / SULCRATE SUSPENSION PLUS used for?

SULCRATE Tablets are used to:

- treat duodenal ulcers. These are open sores that form in part of the small intestine called the duodenum. The duodenum is where food goes after it leaves the stomach.
- treat non-cancerous stomach ulcers. These are open sores that form in the stomach lining but are not caused by cancer.
- prevent duodenal ulcers from coming back after previous treatment.

SULCRATE SUSPENSION PLUS is used to:

- treat duodenal ulcers.
- prevent bleeding in the digestive system due to stress ulcers in very sick patients.

How does SULCRATE / SULCRATE SUSPENSION PLUS work?

SULCRATE / SULCRATE SUSPENSION PLUS contains sucralfate, which works to create a protective barrier around the ulcer. In the body, sucralfate forms a gel that sticks to the ulcer's surface. This barrier protects the ulcer from stomach acids and helps it heal.

What are the ingredients in SULCRATE / SULCRATE SUSPENSION PLUS?

Medicinal ingredients: Sucralfate

SULCRATE Tablets non-medicinal ingredients: Calcium carboxy-methylcellulose, hydrogenated vegetable oil, magnesium stearate and microcrystalline cellulose

SULCRATE SUSPENSION PLUS non-medicinal ingredients: Butterscotch artificial flavour, glycerine, sodium methylparaben, sodium phosphate monobasic, sodium propylparaben and xanthan gum

SULCRATE / SULCRATE SUSPENSION PLUS comes in the following dosage forms:

Tablets: 1 gram (g)
Oral Suspension: 1 g/5 mL

Do not use SULCRATE / SULCRATE SUSPENSION PLUS if:

- you are allergic to sucralfate.
- you are allergic to any ingredient in SULCRATE / SULCRATE SUSPENSION PLUS

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

- have any conditions that make it difficult to swallow.
- have diabetes. Sugars in SULCRATE SUSPENSION PLUS may cause high blood sugar in people with diabetes.
- have chronic kidney failure or receive dialysis. Patients with chronic kidney failure or those receiving dialysis may not be able to get rid of the aluminum in SULCRATE / SULCRATE SUSPENSION PLUS. This can lead to a buildup of aluminum in the body, which can cause confusion, muscle weakness, seizures, and other symptoms.
- are pregnant or trying to become pregnant.
- Are breastfeeding or plan to breastfeed. It is not known if SULCRATE / SULCRATE SUSPENSION PLUS passes in breastmilk.

Other warnings you should know about:

- SULCRATE SUSPENSION PLUS must not be given intravenously (placed directly into a vein, also called IV). If SULCRATE SUSPENSION PLUS is injected into a vein by mistake, it can cause serious issues such as blood clots in the heart and brain, which can cause death. Other serious issues have been seen in patients after an accidental injection into a vein.

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 SULCRATE / SULCRATE SUSPENSION PLUS:

- some medicines used to treat heartburn and indigestion called antacids.
- a medicine used to prevent seizures or to treat epilepsy called phenytoin.
- a medicine that thins blood called warfarin.
- a medicine used to treat heart conditions called digoxin.
- an antibiotic medicine used to treat bacteria infections called tetracycline.
- some fluoroquinolone antibiotics used to treat bacteria infections like ciprofloxacin and norfloxacin.
- some medicines used to reduce pain called naproxen, indomethacin or ketoprofen

How to take SULCRATE / SULCRATE SUSPENSION PLUS

SULCRATE Tablets:

- take on an empty stomach.
- take SULCRATE Tablets for as long as your healthcare professional tells you to take them.

SULCRATE SUSPENSION PLUS:

- take on an empty stomach,
- take orally (by mouth) or via nasogastric tube for the prevention of bleeding in the digestive system.
- take SULCRATE SUSPENSION PLUS for as long as your healthcare professional tells you to take them.

Usual dose:

SULCRATE Tablets:

Duodenal ulcer:

- One 1 g tablet, four times a day, one hour before meals and one at bedtime or
- Two 1 g tablets, twice daily, when waking up and at bedtime.

Non-cancerous stomach ulcer:

- One 1 g tablet, four times a day, one hour before meals and one at bedtime.

Prevent duodenal ulcers from coming back:

- One 1 g tablet, twice daily, when waking up and at bedtime.

SULCRATE SUSPENSION PLUS:

Duodenal ulcer:

- 2 g (2 teaspoons or 10 mL), twice a day, when waking up and at bedtime.

Prevent bleeding in the digestive system:

- 1 g (1 teaspoon or 5 mL) by mouth or through nasogastric (NG) tube every 4 to 6 hours
- 1 g (1 teaspoon or 5 mL) through a thin tube placed through the nose and into the stomach (called a nasogastric or NG tube) every 4 to 6 hours

Overdose:

An overdose is when you take more medicine than what has been prescribed by your doctor. If you have an overdose of SULCRATE / SULCRATE SUSPENSION PLUS, you may have constipation.

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

Missed Dose:

If you forget to take your medicine, take it as soon as you remember. However, if it's almost time for your next dose, just wait and take that dose at its regular time. Never take two doses of the medicine at once.

What are possible side effects from using SULCRATE / SULCRATE SUSPENSION PLUS?

These are not all the possible side effects you may have when taking SULCRATE / SULCRATE SUSPENSION PLUS. If you experience any side effects not listed here, tell your healthcare professional.

SULCRATE Tablets:

- Back pain
- Constipation
- Diarrhea
- Dizziness
- Dry mouth
- Indigestion (pain, gas, burning feeling, or discomfort after eating)
- Nausea
- Sleepiness
- Stomach pain
- Vertigo (feeling that you or the room you are in is spinning)

SULCRATE SUSPENSION PLUS:

- Constipation
- Diarrhea
- Headache
- Nausea
- Stomach pain
- Urticaria

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: trouble breathing, chest tightness, hearing a whistling sound while breathing, itching, rash, hives, swelling around the face, mouth, throat, lips, or eyes			✓
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue. (This is related to SULCRATE SUSPENSION PLUS only)		✓	

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

Reporting Side Effects

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

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

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

Storage:

Store between 15 and 30°C. Protect SULCRATE SUSPENSION PLUS from freezing.

Keep out of reach and sight of children.

If you want more information about SULCRATE / SULCRATE SUSPENSION PLUS:

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

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