PRODUCT MONOGRAPH

PrSULCRATE®

(sucralfate)

1 g Tablets

PrSULCRATE® SUSPENSION PLUS

(sucralfate)

1 g/5 mL Oral Suspension

Gastro-Duodenal Cytoprotective Agent

APTALIS PHARMA CANADA ULC 85 Enterprise Blvd., Suite 500 Markham, Ontario L6G 0B5	Date of Preparation: September 12, 2013 Date of revision: July 27, 2016
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THERAPEUTIC CLASSIFICATION

Gastro-Duodenal Cytoprotective Agent

ACTIONS AND CLINICAL PHARMACOLOGY

SULCRATE® (sucralfate) exerts a generalized gastric cytoprotective effect by enhancing natural mucosal defence 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.

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.

INDICATIONS AND CLINICAL USE

1. **Tablets**

   SULCRATE® (sucralfate) tablets are indicated for the treatment of duodenal and non-malignant gastric ulcer.

   SULCRATE® tablets are also indicated for the prophylaxis of duodenal ulcer recurrence.

2. **Suspension**

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.

CONTRAINDICATIONS

Patients with known hypersensitivity to the active substance or to any of the excipients.

The physician should read the "WARNINGS" section when considering the use of this drug in pregnant or pediatric patients, or patients of childbearing potential.

WARNINGS

Use in Pregnancy

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.

Pediatric Use

Clinical experience in children is limited. Therefore, sucralfate therapy cannot be recommended for children under 18 unless, in the judgment of the physician, anticipated benefits outweigh the potential risk.

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 aluminium 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.

Drug Interactions

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.

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.

In clinical trials, the concomitant administration of sucralfate reduced the bioavailability of digoxin. In case of simultaneous administration, the extent of absorption of phenytoin, warfarin, and fluoroquinolone antibiotics (e.g. ciprofloxacin and norfloxacin) is also reduced. These interactions appear to be non-systemic and to result from the binding of sucralfate the concomitantly administered drug in the gastrointestinal tract. In all cases, complete bioavailability was restored by separating the administration of sucralfate from that of the other agent by 2 hours.

Sucralfate, administered respectively 30 and 60 minutes before ASA or ibuprofen did not alter the bioavailability of these agents. In a study comparing the prior administration of a single dose of sucralfate tablets on the bioavailability of naproxen, indomethacin or ketoprofen versus administration in the absence of sucralfate, it was shown that the total amount of these drugs absorbed was not altered; however, the peak concentration of each was reduced, and the time to reach peak concentration was delayed. A single dose of SULCRATE® SUSPENSION PLUS administered one-half hour before naproxen had a similar effect on the bioavailability of naproxen.

The physician 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.

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 ACTIONS AND CLINICAL PHARMACOLOGY). 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 μg/L after one week of treatment from a pretreatment level of 3 μg/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 physician discretion since the excretion of absorbed aluminum may be impaired in these individuals.

ADVERSE REACTIONS

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.

1. **SULCRATE® Tablets**

Very few side effects have been reported with SULCRATE® (sucralfate) 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.

Bezoars have been reported in patients treated with sucralfate (SULCRATE® tablets). 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.

2. **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.

Bezoars have also been reported in patients treated with sucralfate (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.

See the PRECAUTIONS section 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage has never been observed with SULCRATE® (sucralfate) 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 ADVERSE REACTION section, such as constipation. These should be treated symptomatically.

For management of suspected drug overdose, contact your regional Poison Control Center.

DOSAGE AND ADMINISTRATION

1. **Tablets**

   The recommended adult oral dosage of SULCRATE® (sucralfate) for duodenal and gastric ulcer is one tablet of 1 g 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.

   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.

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.

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 hour before or after SULCRATE® intake.

2. **Suspension**

SULCRATE® SUSPENSION PLUS (1 g/5 mL)

SULCRATE® must not be administered intravenously.

The recommended adult dose of SULCRATE® SUSPENSION PLUS for the treatment of (acute) duodenal ulcer is 2 g (10 mL) twice a day on waking and at bedtime on an empty stomach.

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.

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 PRECAUTIONS). According to information widely available in the literature, patients with serum aluminum concentrations that approach 100 μg/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. Physician discretion should be exercised when considering the duration of treatment (see PRECAUTIONS).

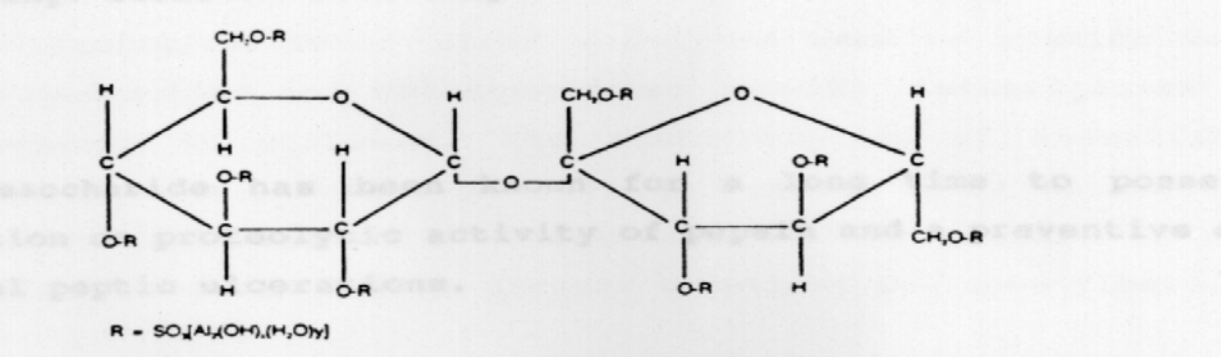
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: sucralfate

Chemical name: $C_{12}H_{14}0_{35}S_8$ $8[Al_2(OH)_x]$

Structural formula:



Physical Characteristics: Sucralfate occurs as a white to slightly yellowish white, amorphous powder.

CHEMISTRY

Sucralfate is an aluminum salt of a sulfated disaccharide. Chemically it is 3,4,5,6-Tetra-(polyhydroxyaluminum)-alpha-D-glucopyranosylsulfate-2,3,4,5,-tetra-(polyhydroxyaluminum)-beta-D-fructofuranoside sulfate ($C_{12}H_{14}0_{35}S_8$ $8[A1_2(OH)_x]$).

It is soluble in dilute hydrochloric acid and sodium hydroxide but practically insoluble in water, boiling water, ethanol or chloroform.

Composition:

Each SULCRATE® tablet contains 1 g of sucralfate. Each tablet also contains as non-medicinal ingredients: hydrogenated vegetable oil, calcium carboxy-methylcellulose, magnesium stearate and microcrystalline cellulose.

Each 5 mL of suspension contains 1 g of sucralfate. The suspension also contains as non-medicinal ingredients: glycerine, sodium methylparaben, sodium propylparaben, sodium phosphate monobasic, xanthan gum, caramel artificial flavour.

Stability and Storage Recommendations:

SULCRATE® SUSPENSION PLUS should be stored at room temperature between 15 and 30°C. Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

1. **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.

   To be kept and dispensed in a well-closed container. Bottles of 100 tablets.

2. **Suspension**

   SULCRATE® SUSPENSION PLUS

   Each 5 mL of off-white, creamy, suspension with a caramel odour contains 1 g of sucralfate. Supplied in bottles of 500 mL. Shake well before using.

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.

1. **Antiulcerogenic Activity**

   Studies in rats involving the action of sucralfate against ulcers induced by pyloric ligation revealed that the drug reduces the incidence and size of the lesions 80-90% at single doses of 30 to 50 mg/rat. Other studies using rat restraint and stress models showed a similar level of protection with single doses of 50 to 400 mg/rat. In addition, the drug was effective in reducing the number of hemorrhagic areas.

   Thermocautery-induced ulcers in the rat were used to demonstrate the promotion of mucosal regenerating activity of 200 mg of sucralfate. In addition, a quantity of 5 mg sucralfate was found to hinder the digestion on the gastric mucosa by gastric juice in vitro.

   The rat clamping/cortisone ulcer model was used to examine healing, mucosal regeneration and collagen fiber growth. Investigators showed that, compared to controls, the administration of sucralfate was associated with an increase of 161% in healing index as measured by the degree of contraction of the ulcer, a 132% increase in mucosal regeneration index and a 100% greater growth of collagen fibers.

   Another series of experiments was conducted involving rat models where ulcers were induced by acetic acid, pylorus ligation, prednisolone, reserpine and restraint. In the acetic acid model, the presence of sucralfate at a dose of 500 mg/kg/day significantly reduced the ulcer index approximately 44% based on surface area measurement of the ulcer. Similar results were obtained in the restraint test, 100 and 200 mg reduced the ulcer index as measured by the number of rats with ulcers, the total number of ulcers and ulcer severity in the prednisolone and reserpine

models at least 53% and 84%, respectively. At 50 and 100 mg ulcer index was decreased 80% and 100%, respectively, in the pyloric ligation model.

When histamine injection was used to elicit ulcers in guinea pigs, administration of 200 and 400 mg sucralfate reduced the incidence of gastric ulcers by approximately 90% as compared to the untreated controls. Parallel responses were seen in terms of the duodenal lesions.

2. **Mechanism of Action**

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 E_2 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:

1) Formation of a chemical complex that binds to the ulcer site to establish a protective barrier.
2) Direct inhibition of the action of pepsin and bile.
3) 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.

3. **Clinical Experience**

Duodenal Ulcer

The safety and efficacy of SULCRATE® (sucralfate) 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.

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

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. Endoscopic evaluations at 6 and 12 months showed the following incidences of recurrence: at 6 months, 20% of SULCRATE® treated patients had recurred, compared to 74% of patients treated with a placebo. At 12 months, the recurrence rate for patients receiving SULCRATE® tablets was 27%, compared to 80% in patients receiving a placebo. 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

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

TOXICOLOGY

1. **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.

2. **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.

3. **Chronic Toxicity - 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.

4. **Reproduction and Teratology**

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.

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