PRODUCT MONOGRAPH

[Pr]TEVA-SUCRALFATE
(Sucralfate Tablets, USP)

1g

Gastro-Duodenal Cytoprotective Agent

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1g

THERAPEUTIC CLASSIFICATION

Gastro-Duodenal Cytoprotective Agent

ACTIONS AND CLINICAL PHARMACOLOGY

TEVA-SUCRALFATE (sucralfate) enhances the natural mucosal defense mechanisms, thereby producing a generalized gastric cytoprotective effect. The ability of sucralfate to protect the gastric mucosa against various irritants, such as alcohol, ASA, hydrochloric acid, sodium hydroxide or sodium taurocholate, has been demonstrated in animal studies and in clinical trials in humans. It has also been shown that sucralfate has a greater affinity for ulcerated gastric or duodenal mucosa than for non-ulcerated mucosa.

An adherent cytoprotective barrier is produced by sucralfate at the site of the ulcer, thereby protecting it from the potential ulcerogenic properties of acid, pepsin and bile. Acid diffusion across the sucralfate-protein barrier is blocked by sucralfate. Evidence suggests that sucralfate also complexes directly with pepsin and bile.

The mode of action of sucralfate is non-systemic; only minimal amounts of the drug are absorbed from the gastrointestinal tract following oral administration. The minute amounts of sucralfate which are absorbed are eliminated primarily in the urine.

Each gram of sucralfate contains approximately 200 mg of aluminum. At low pH the aluminum moiety can dissociate and aluminum release can be expected; however, aluminum is poorly absorbed from the intact gastrointestinal tract. In patients with normal renal function, administration of 1g of sucralfate four times a day resulted in approximately 0.001% to 0.017% of the aluminum content of sucralfate to be absorbed and excreted in the urine. This is equivalent to 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. Evidence available to date does not indicate that absorption of aluminum would be different in individuals with ulcerated gastrointestinal mucosa.

Experiments have demonstrated that sucralfate is not an antacid.

INDICATIONS AND CLINICAL USE

TEVA-SUCRALFATE (sucralfate) is indicated in the treatment of duodenal and nonmalignant gastric ulcer. TEVA-SUCRALFATE is also indicated for the prophylaxis of duodenal ulcer recurrence.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate. However, when considering the use of TEVA-SUCRALFATE in pregnant or nursing women, women of childbearing potential, or pediatric patients, the physician should read the WARNINGS section.

WARNINGS

Use in Pregnancy: Since there has been no experience with the use of sucralfate in pregnant women to date, TEVA-SUCRALFATE (sucralfate) should not be administered to pregnant or nursing women or women of childbearing potential unless, in the judgment of the physician, the anticipated benefit outweighs the potential risk.

Use in Pediatric patients: There is limited clinical experience with sucralfate in children. The administration of TEVA-SUCRALFATE to children less than 18 years of age can therefore not be recommended unless, in the judgment of the physician, the anticipated benefits outweigh the potential hazards.

PRECAUTIONS

Since the symptomatic response to TEVA-SUCRALFATE (sucralfate) does not preclude the presence of gastric malignancy, proper diagnosis is important.

Drug Interactions:

Sucralfate should not be taken within half an hour before or after antacids, since the change in intragastric pH may decrease the binding of sucralfate with the gastroduodenal mucosa.

Animal studies have shown that sucralfate, administered simultaneously with tetracycline, phenytoin or cimetidine, results in a statistically significant reduction in the bioavailability of the agents. Cimetidine absorption was not reduced in humans. The concomitant administration of sucralfate to healthy humans reduced the mean AUC value of digoxin by about 19%. However, the bioavailability of ASA and ibuprofen are unaltered when sucralfate is administered respectively, 30 and 60 minutes before these agents.

Apparently, these interactions are non-systemic and result from the binding of sucralfate to the concomitantly administered drug in the gastrointestinal tract. By separating the administration of sucralfate from that of the other agent by 2 hours, complete bioavailability was restored in all cases. As such, the separation of the administration of any drug from that of sucralfate is recommended and the potential clinical significance of any interaction should be considered.

Patients may experience recurrence of gastric or duodenal ulcer. Although treatment with TEVA-SUCRALFATE can produce complete healing, a successful course of treatment should not be expected to alter the underlying cause of ulcer disease.

Chronic Renal Failure

Dialyzed Patients - Sucralfate should be used with caution in patients with chronic renal failure. When administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract (see ACTIONS AND CLINICAL PHARMACOLOGY). Current 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 those individuals, aluminum is known to accumulate in serum and in tissues. Dialysis patients in particular 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.

There have been reports of aluminum-related toxicity (encephalopathy and aluminum-related bone disease), associated with the administration of sucralfate and/or other sources of aluminum in patients with chronic renal failure undergoing dialysis. 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 μlg/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. There were no reports of adverse events in these patients.

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

ADVERSE REACTIONS

Very few side effects have been reported with sucralfate. The reactions associated with this drug have generally been mild and have rarely led to the discontinuation of therapy.

Constipation was the primary complaint and has been reported in 1.4 to 2.6% of the patients treated with sucralfate.

Other side effects that have been reported in association with sucralfate included diarrhea, nausea, vomiting, flatulence, gastric discomfort, indigestion, dry mouth, skin rash, pruritus, back pain, dizziness, headache, sleepiness and vertigo.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with sucralfate has never been observed. A lethal dose could not be established using maximal doses of up to 12 g/kg body weight in various animal species; therefore, overdosage appears to be unlikely.

It is likely that overdosage would be associated with symptoms similar to those described in ADVERSE REACTIONS, such as constipation, and symptomatic treatment would be indicated.

DOSAGE AND ADMINISTRATION

Treatment of Duodenal and Non Malignant Gastric Ulcer

The recommended adult oral dosage for duodenal and non malignant gastric ulcer is one 1 g tablet four times daily, one hour before meals and at bedtime. TEVA-SUCRALFATE (sucralfate) should be taken on an empty stomach. For duodenal ulcer, TEVA-SUCRALFATE may also be administered as two 1 g tablets twice daily, on waking and at bedtime on an empty stomach.

Antacids may be added to the treatment regimen for the relief of pain. However, antacids should not be taken within one-half hour before or after sucralfate.

With duodenal ulcers, healing often occurs within 2 to 4 weeks; however, treatment should be continued for 8 to 12 weeks unless healing has been demonstrated by x-ray and/or endoscopic examinations.

With non malignant gastric ulcers, an alternate treatment should be considered if an objective improvement is not observed after 6 weeks of therapy. However, a longer treatment period may be required in patients with a large gastric ulcer that has demonstrated a progressive healing tendency.

Prophylaxis of Duodenal Ulcer

The recommended dosage for the prophylaxis of duodenal ulcer recurrence is one tablet of 1 g twice daily on an empty stomach. Treatment may be continued for up to one year.

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). Current evidence indicates that 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 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).

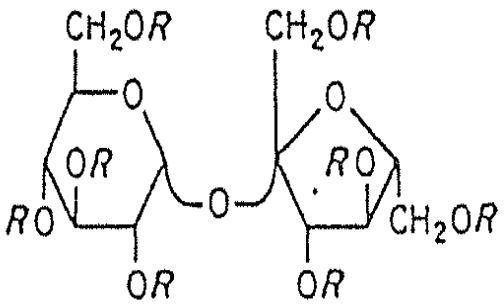
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Sucralfate

Chemical Name: α-D-Glucopyranoside,β-D-fructofuranosyl-octakis(hydrogen sulfate), aluminum complex.

Structural Formula:



(*R* is $SO_3(A1_2(OH)_{\%}(H_20)_y]$)

Molecular Formula: $C_{12}H_mAI_{16}0_nS_8$

Description: Sucralfate is an aluminum metal salt of a sulfated disaccharide. It is a whitish or white, odourless, amorphous powder which is soluble in dilute hydrochloric acid and sodium hydroxide, but practically insoluble in water, boiling water, ethanol or chloroform. The pH is in the range of 5-6.

STABILITY AND STORAGE RECOMMENDATIONS:

Store at 15-30°C. Unit dose strips should be stored at 15-25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-SUCRALFATE (sucralfate) is available as white, capsule-shaped, bi-convex compressed tablets, one side plain, the other side engraved with **novo** inside a raised border. Each tablet contains 1 g sucralfate.

Supplied: Bottles of 100 and 500 and in boxes of 100 as unit dose strips.

PHARMACOLOGY

Distinct morphologic and functional changes are produced in the normal gastric mucosa by sucralfate including mucus release, changes in ion transport and increased release of luminal prostaglandins. Several studies have demonstrated that sucralfate can increase the synthesis and release of prostaglandin E_2 from the mucosa, which may partially explain its cytoprotective properties.

Polysaccharide sulfates possess an inhibitory action on the proteolytic actions of pepsin and a preventative action on experimental peptic ulcerations. Sucralfate is a disaccharide sulfate which has demonstrated strong antipepsin and antiulcer action.

In contrast to the more polymerized saccharides, sucralfate is devoid of any anticoagulant activity. The enhanced antiulcerogenic activity is also more pronounced with the aluminum salt of sucralfate. Sucralfate has no apparent effect on the cardiovascular system, the central nervous system, or on the hematopoietic system, including blood coagulation factors.

Antiulcerogenic Activity

In rat studies, single doses of sucralfate 150 to 250 mg/kg reduced the incidence and size of ulcer lesions induced by pyloric ligation. In other studies in rats using restraint and stress models, a similar level of prophylaxis was observed with single doses of 200 to 2000 mg/kg. The drug was also effective in reducing the number of hemorrhagic areas.

The promotion of mucosal regenerating activity of sucralfate 1000 mg/kg was demonstrated in rats with thermocautery-induced ulcers. Also, sucralfate was found to hinder the digestion of gastric mucosa by gastric juice *in vitro.*

Sucralfate was reported to promote mucosal regeneration in rats with clamping/cortisone induced ulcers. It was reported that the administration of sucralfate was associated with an increase of 161% in the healing index as measured by the degree of contraction of the ulcer, a 132% increase in the mucosal regeneration index and a 100% increase in the growth of collagen fibres compared to controls.

In another series of experiments in rats, ulcers were induced by acetic acid, pyloric ligation, prednisolone, reserpine and restraint. In the acetic acid study, the ulcer index based on surface area-measurement of the ulcer, was reduced significantly (44%) by the administration of sucralfate 500 mg/kg/day. The results of the restraint test were similar and, in the prednisolone and reserpine tests, 500 and 1000 mg/kg sucralfate reduced the ulcer index as measured by the number of rats with ulcers, the total number of ulcers and ulcer severity at least 53% and 84%, respectively. In the pyloric ligation experiment, the ulcer index was also significantly decreased.

When histamine injection was used to elicit ulcers in guinea pigs, the administration of 1000 and 2000 mg/kg sucralfate reduced the incidence of histamine-induced gastric ulcers by approximately 90%. Parallel responses were observed with duodenal lesions.

In vivo and *in vitro* studies have shown that sucralfate produced an adherent and cytoprotective barrier at the ulcer site which resists degradation by acid and pepsin.

The binding ability of sucralfate was demonstrated in rats with experimentally-induced ulcers. The animals were given a single dose of sucralfate, after which the ulcerated organs were excised and washed with a fluorescent compound which was taken up by sucralfate. The sucralfate showed an affinity for the areas of ulceration, thereby supporting the binding action of the drug.

The affinity of sucralfate for the ulcer site was further substantiated in a study with patients scheduled for gastric resection. All of the patients received the same daily dose of sucralfate, but the time interval between the last dose and the surgical procedure was variable (2 to 16 hours). At all the time intervals, the concentration of sucralfate in the ulcer craters was higher than concentrations in tissue samples taken from normal mucosa in the same patient.

Several *in vitro* and *in vivo* studies have demonstrated the anti-pepsin activity of sucralfate.

In *in vitro* studies on pylorus ligated rat models, pepsin activity of the gastric juice was inhibited, the total acidity was reduced, and the pH of the gastric fluid was increased in the presence of sucralfate.

In ulcer patients, the effects of sucralfate on pepsin activity were monitored for 30 minutes following the ingestion of the drug. Doses of 1, 1.5, 2, 2.5, and 3 g decreased pepsin activity by 32, 34, 44 and 55%, respectively.

Sucralfate has been shown to decrease bile salt concentrations *in vitro* by adsorbing the bile salts onto sucralfate in suspension. Glycocholic acid in a buffered solution was used in this test and the maximum adsorption was found to be approximately 112 mg per gram of sucralfate.

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

The ability of sucralfate to block acid diffusion was further substantiated in a clinical study. Normal volunteers received either sucralfate followed by glycocholic acid or glycocholic acid alone. The gastric transmural potential difference was then measured.

The decrease in the potential difference produced by glycocholic acid was reduced by sucralfate, indicating a decrease in back diffusion of acid.

Clinical Results

A randomized, single-blind (investigator), multi-centre, parallel clinical trial was conducted to compare the safety and efficacy of TEVA-SUCRALFATE (sucralfate) Tablets and Sulcrate® (sucralfate) Tablets (Nordic). One hundred and fifteen patients with symptoms of gastric and/or duodenal ulcers and an endoscopically proven benign ulcer crater were randomized to one of the two treatment groups. Following an admission examination, patients took the appropriate study medication orally (within 24 hours of endoscopy) 4 times daily, one hour before meals and at bedtime, on an empty stomach. Patients returned for interim examinations after 2 and 4 weeks. Patients whose ulcers were not healed (determined by endoscopic examination) by week 4 were instructed to continue treatment for an additional 4 weeks and return for a final examination after a total of 8 weeks of treatment.

The primary efficacy parameter was ulcer healing, with definitive confirmation on healing being determined by endoscopic results. Healing was defined as complete re-epithelization of the largest ulcer crater. Secondary efficacy parameters included the frequency of daytime or nighttime pain episodes, the severity of each daytime or nighttime pain episode, duration of each pain episode and the daily consumption of study antacid tablets.

The following healing rates, regardless of smoking history, were calculated at 4 and 8 weeks.

Ulcer Type	**Week 4**		**Week 8**	
	Test	**Reference**	**Test**	**Reference**
Duodenal	63.04%	56.25%	81.82%	84.09%
Gastric	36.36%	60.00%	54.55%	80.00%
Combined	57.89%	56.60%	76.36%	83.67%

It should be noted gastric ulcer healing rates were based on only 16 patients. There were no statistically significant differences found between the test formulation treatment group and the reference formulation treatment group for any classification of ulcer healing rate or for any of the Secondary parameters.

The assessment of safety parameters revealed no significant differences between the two treatment groups and, with the exception of SGPT activity, none of these parameters exhibited any significant change over time. Although SGPT activity did significantly decrease over time for both treatment groups, the SGPT activity for both treatment groups at weeks 2, 4 and 8 was still well within the normal range.

Based on the results of this study, it can be concluded that no significant differences in efficacy and safety exist between the test formulation of sucralfate and the reference formulation of sucralfate in the treatment of acute duodenal or gastric ulcers.

TOXICOLOGY

Acute Toxicity:

Sucralfate was considered to have low acute toxicity in the rat when administered orally, with the LD_{50} greater than 12 g/kg. This finding was not unexpected in the light of the very low oral absorption.

Chronic Toxicity:

A six month oral toxicity study was conducted in rats with doses of up to 4 g/kg/day. There was a dose related incidence of fibrous hyperplasia of the mucosal and sub-mucosal layers of the stomach. Renal changes described as degeneration or loss of tubular epithelial cells were also observed at the highest dosage level.

In rabbits given doses of up to 1 g/kg/day for 1 month, mucosal edema and hemorrhage in the colon and rectum were observed along with a slight increase in bloody stools. There was also an increase in reticulocytes at the highest dose and a slight dose related nephrosis in the females only.

In a 12 month oral study in dogs with doses of up to 500 mg/kg/day, the only drug related toxicity observed was foamy vacuolation of the cytoplasm of the epithelial cells in the proximal convoluted tubules of the kidneys at the 250 and 500 mg/kg/day dosage levels. These changes were reversible within 7 days after the cessation of drug treatment and kidney function was not affected.

A 24 month oral toxicity study was conducted in mice and rats at doses of up to 1 g/kg/day. An increase in extramedullary hematopoiesis was seen at the 1 g/kg/day dosage level in both species. No drug related tumorigenicity was observed.

Reproduction and Teratology:

All three segments of reproduction studies were conducted in mice, rats and rabbits and were generally unremarkable.

In one teratology study conducted in rabbits, maternal toxicity (maternal weight loss) was observed at the highest dose of 1 g/kg/day, which was the result of a marked decrease in food consumption. This resulted in a significant reduction in the average fetal weight and a slight decrease in the 24 hour neonatal viability.

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