SUCRALFATE

ISELPIN®

1 g Tablet

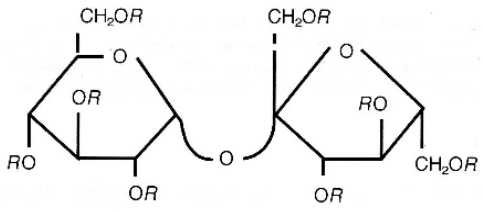
1.0 PHARMACOLOGIC CATEGORY

Cytoprotector

2.0 DESCRIPTION

Sucralfate is a white, amorphous powder which is soluble in strong acids and in alkalis but practically insoluble in water and in alcohol. It is a basic, aluminum complex of sucrose octasulfate.

Sucralfate has the chemical name, α-D-Glucopyranoside β-D-fructofuranosyl, octakis (hydrogen sulfate), aluminum complex. Its molecular formula is $C_{12}H_mAl_6O_nS_8$ ($_m$ and $_n$ are approximately 54 and 75 respectively, resulting in an average molecular weight of about 2086 daltons). Its chemical structure is:



(*R* is $SO_3[Al_2(0H)_X(H_20)_Y]$)

3.0 FORMULATION

Each tablet contains 1 g of Sucralfate.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sucralfate is indicated for the treatment of gastric and duodenal ulcer and chronic gastritis

It is also indicated for the relapse prophylaxis of gastric and duodenal ulcer, and treatment of reflux oesophagitis, and the prophylaxis of stress ulcer.

4.2 Dosage and Method of Administration

The recommended adult oral dosage is 1 g four times a day on an empty stomach (1 hour before each meal and at bedtime).

Antacids may be used as needed for relief of pain but should not be taken within 30 minutes before or after Sucralfate.

Although healing with Sucralfate may occur during the first week or two, continuation of treatment is suggested for 4-8 weeks unless healing has been demonstrated by X-ray or endoscopic examination. In resistant cases, up to 12 weeks may be needed.

Sucralfate (Iselpin) must not be administered intravenously.
Application via the enteral tube
After application of sucralfate (Iselpin) via the enteral tube, the tube has to be flushed with 10 to 15 ml of water, to prevent closure of the tube. (see **section 4.8 Undesirable Effects**)

4.3 Contraindications

1. Individuals with a known hypersensitivity to any of the ingredients.
2. Patients receiving dialysis (Long-term administration of this product may result in aluminum accumulation and toxicity. Aluminum toxicity has been implicated in encephalopathy and osteomalacia).

4.4 Special Warnings and Precautions for Use

Do not administer intravenously.
Sucralfate (Iselpin) 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.

Chronic renal impairment
Sucralfate is not recommended for use in individuals on dialysis.

Sucralfate should be administered carefully in patients with chronic impairment of renal function. Small amounts of aluminium are absorbed through the gastrointestinal tract and aluminium may accumulate. Aluminium osteodystrophy, osteomalacia, encephalopathy, and anaemia have been reported in patients with chronic renal impairment. For patients with impairment of renal function (chronic renal failure, etc.) laboratory testing such as aluminum phosphate, calcium and alkaline phosphatase is recommended to be periodically performed due to excretion impairment.

Swallowing difficulty
At the time of taking sucralfate tablets, aspiration may occur in patients with swallowing difficulty.
Pediatric Use
Safety and effectiveness in children have not been established.

Geriatric Use
Since physiologic functions are usually reduced in elderly patients, caution must be exercised with careful consideration given to the dosage.
While short-term (usually up to 8 weeks) treatment can completely heal the ulcer, this disease state is a chronic and recurrent one. Sucralfate cannot be expected to alter the post-healing frequency or severity of ulceration.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

Concomitant administration of sucralfate may reduce the bioavailability of certain drugs including fluoroquinolones, digoxin, ketoconazole, sulpiride, levothyroxine and phenytoin, and possibly warfarin and sustained released theophylline.

About ketoconazole and sulpiride, the bioavailability of these agents may be restored by separating the administration of these agents from sucralfate by 2 hours.

The bioavailability of fluoroquinolones may be restored when fluoroquinolones are administered 2 hours prior to sucralfate. It has been reported in clinical trials on healthy volunteers that the bioavailability of norfloxacin is reduced 2 hours after sucralfate.

Sucralfate should not be coadministered with citrate preparations. Coadministration of citrate preparations with sucralfate may increase the blood concentrations of aluminium. The mechanism may be due to chelation of aluminium, which is assumed to increase its absorption.

4.6 Fertility, Pregnancy and Lactation

The safe use of sucralfate during pregnancy has not been established. The studies in animals have not shown teratogenicity (see **section 5.3 Preclinical Safety Data**).

The safe use of sucralfate during lactation has not been established.

4.7 Effects on Ability to Drive and Use Machines

The pharmacodynamic profile of sucralfate does not indicate that the effect on the ability to drive and use machines are expected.

4.8 Undesirable Effects

The following categories of frequency of adverse reactions are used: Very common (≥ 10%); common (≥ 1% and < 10%); uncommon (≥ 0.1% and <1%); rare (≥ 0.01% and <0.1%); very rare (< 0.01%)

Immune system disorders
Unknown: anaphylactic reaction including pruritus, urticaria, oedema and dyspnoea.

Gastrointestinal disorders
Common: constipation,
Uncommon: dry mouth, nausea,
Rare: Bezoar formation has been reported in patients with impaired gastric emptying, patients with enteral tube feeding or low birthweight infants.

Skin and subcutaneous tissue disorders
Rare: rash.

Injury, poisoning and procedural complications
Small amount of aluminium is absorbed through the gastrointestinal tract and aluminium may accumulate. Aluminium osteodystrophy, osteomalacia, encephalopathy, and anaemia have been reported in patients with chronic renal impairment (See **section 4.4 Special Warnings and Precautions for Use** – *Renal Impairment*).

4.9 Overdose

In a clinical trial on healthy men of overdose with sucralfate, most cases remained asymptomatic, but symptoms of abdominal pain, nausea, and vomiting were reported in a few cases.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

When sucralfate was administered orally to patients with peptic ulcer or gastritis, it was observed that it bound strongly to ulcerated or inflamed lesions. It is thought that sucralfate binds strongly to proteins in inflamed mucosa or exudate at the base of ulcers to form a chemical layer, that protects lesions from the potent digestive action of gastric juices and accelerating healing.

The results of animal experiments (rats) confirmed that sucralfate inhibits pepsin activity in gastric juice.

The results of animal experiments (rats) showed that sucralfate weakens acids.

Clinical / Efficacy Studies

Japanese clinical study was performed on 1216 patients with gastric ulcer by oral administration with sucralfate granule by 3 to 4 g daily for 8 weeks. As the results based on observation by endoscopic examinations, the cure rate was 270 / 913 patients (29.6%) 4 weeks after administration start, and 541/752 patients (71.9%) 8 weeks after.

Japanese clinical study was performed on 667 patients with duodenal ulcer by oral administration with sucralfate by 3 to 4 g daily for 8 weeks. As the results based on observation by endoscopic examinations, the cure rate was 321 /667 patients (48.1%) 4 weeks after administration start, and 535/667 patients (80.2%) 8 weeks after.

Japanese double-blind controlled trial was performed on 298 patients with acute gastritis or chronic gastritis in the acute exacerbation phase. Among them, 143 patients were treated by oral administration with sucralfate granule by 900 mg t. i. d. for 4 weeks, and 144 patients with cetraxate by 200mg q. i. d. for 4 weeks. As the results based on observation by endoscopic examinations, the cure rate on sucralfate treatment was 68 / 98 patients (69.4%) 2 weeks after administration start, and 73 / 91 patients (80.2%) 4 weeks after. However the difference between sucralfate and cetraxate was not significant.

Japanese clinical studies were performed on 75 patients with gastric ulcer, 70 patients with duodenal ulcer, and 105 patients with acute or chronic gastritis in the acute exacerbation phase by oral administration with sucralfate suspension by 3 g daily for 8 weeks, 6 weeks, and 2 weeks, respectively. It was concluded that the treatment was beneficial in each study.

A double-blind multicenter, randomized study was performed in 70 patients with endoscopically documented reflex esophagitis. Patients were randomly given 1 g sucralfate four times a day or the combination of sucralfate 1 g three times a day and 400 mg cimetidine at night. After healing of the esophagitis, patients were randomly given either sucralfate maintenance 2 g daily or placebo for a period of six months. Endoscopy was performed at the beginning of the study after eight weeks, and, in cases with no healing after 16 weeks of therapy. Sixty-three of the 70 patients who initially entered the study could be evaluated after eight weeks. Both groups showed good symptomatic improvement, and no side effects necessitated withdrawal of subjects. Endoscopy showed complete healing in 19.4% of the sucralfate group and in 21.9% of the combination sucralfate and cimetidine group. Endoscopic improvement was found in 50% of the sucralfate group and in 50% of the combination group. After 16 weeks, 56 patients could be evaluated. In the sucralfate group, improvement was seen in 78.6%, and healing in 31%. For the combination group these

values were 59.3% and 37% (not significant). Twenty-six patients entered the maintenance phase of the study; 15 received sucralfate and 11 received placebo. Evaluation of 20 patients after six months showed endoscopic and/or symptomatic relapse of esophagitis in three of 12 patients receiving sucralfate and in two of the eight patients receiving placebo. It is concluded that sucralfate monotherapy in patients with reflux-esophagitis is effective and comparable with a combination of sucralfate during the day and cimetidine at night. No difference was found between sucralfate and placebo in terms of the relapse rate of esophagitis during long-term treatment.

Healing and relapse of acute duodenal ulcer were investigated in an endoscopically controlled multicenter study using a double-blind design. Patients with acute uncomplicated duodenal ulcer were randomly assigned to treatment with sucralfate (1 g four times per day) or ranitidine (150 mg twice per day) for four to eight weeks. After healing, all anti-ulcer treatment was discontinued except for low-dose antacids needed for occasional upper abdominal pain, and the patients were observed for up to one year. Endoscopy was repeated after one year or at any time earlier if symptoms suggested ulcer relapse. Of the 83 patients who entered the study, 75 (sucralfate 40, ranitidine 35) underwent endoscopy after four weeks and could be fully evaluated. Healing rates after four and eight weeks were similar in the two groups (four- and eight-weeks healing rates after sucralfate and ranitidine: 78 and 74%, and 95 and 94%, respectively). Fifty-three patients with healed ulcers (sucralfate 29, ranitidine 24) were observed for up to one year. Duodenal ulcers occurred somewhat later after sucralfate than after ranitidine treatment, but life table analysis showed no significant difference. Thus, the study confirms a similar efficacy of sucralfate and ranitidine in healing of duodenal ulcer. A tendency to delayed relapse early after discontinuation of sucralfate failed to reach statistical significance.

5.2 Pharmacokinetic Properties

Absorption

Sucralfate is only minimally absorbed from the gastro-intestinal tract. The small amounts that are absorbed are excreted primarily in the urine. Absorption of aluminium from sucralfate may be increased in patients on dialysis or with renal impairment.

Elimination

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Pharmacokinetics in Special Populations

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of sucralfate was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of sucralfate was conducted.

5.3 Preclinical Safety Data

Carcinogenicity

Two-year carcinogenicity study in mice found no neoplastic lesions related to sucralfate (0, 50, 250, 1000 mg/kg/day).

Impairment of Fertility
Fertility and reproductive performance in rats were not affected up to 3000 mg/kg/day (0, 60, 450, 3000 mg/kg/day).

Teratogenicity
Teratogenic studies in mice (0, 1000, 3000, 4000 mg/kg/day, dosing from G7 to G12*), rats (0, 50, 250, 1000 mg/kg/day, dosing from G6 to G15) and rabbits (0, 50, 250, 1000 mg/kg/day, dosing from G6 to G18) showed no evidence of teratogenicity. (*G: gestation day)

Other
Rats were well tolerated in 1-month (0, 2000, 4000, 8000 mg/kg/day, twice a day) and 6-month (0, 500, 1000, 2000, 4000 mg/kg/day, once a day) repeated toxicological studies. Major adverse effects observed in both the middle and high dose groups included slight histopathological changes in the stomach such as infiltration of neutrophil in the lamina muscularis mucosae, edema in the submucosa, and slight thickness of the lamina muscularis mucosae.

Dominant lethal study in mice (0, 50, 4000 mg/kg) revealed no increase of dominant lethal rate.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

See outer packaging for the shelf-life of the product

6.2 Storage Condition

Store at a temperature not exceeding 25°C. Keep bottle tightly closed.

6.3 Availability

Sucralfate (Iselpin) 1 g tablet: HDPE Bottle with PP cap x 100's

7.0 FDA REGISTRATION NUMBER

1 g Tablet: DR-XY3501

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

1 g Tablet: 20 Nov 2006

KEEP OUT OF REACH OF CHILDREN.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
INTERPHIL LABORATORIES, INC.
Canlubang Industrial Estate

Bo. Pittland, Cabuyao
Laguna, Philippines

Marketing Authorization Holder:
Pfizer, Inc.
19F-20F, 8 Rockwell Building,
Hidalgo Drive, Rockwell Center, Poblacion,
Makati City, 1210 Metro Manila,
Philippines

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