Mucosal protective and tissue healing agent for gastritis and gastric ulcer

**SOLON® Tablets 50 mg**
**SOLON® Capsules 100 mg**
**SOLON® Fine Granules 20%**
(Sofalcone)

### Storage:
Store at room temperature in a light-resistant container

<table>
<thead>
<tr>
<th>Tablets (50 mg)</th>
<th>Capsules (100 mg)</th>
<th>Fine Granules (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current approval No. (coded in NHI* Drug Price list)</td>
<td>6AM-451 (July 1994)</td>
<td>21300AMZ00646000 (September 2001)</td>
</tr>
<tr>
<td>Marketed in Japan</td>
<td>October 1994</td>
<td>March 1984</td>
</tr>
<tr>
<td>Expiration date: Indicated on the package</td>
<td></td>
<td>August 2004</td>
</tr>
</tbody>
</table>

* NHI: National Health Insurance

### Expiration date:
- International birth date: September 1983 (Japan)
- Indications extended: December 1987
- Reexamination approved: September 1990

### Indications
SOLON is indicated:
- For the management of gastric mucosal lesions (erosion, hemorrhage, redness, or edema) associated with acute gastritis or acute exacerbation of chronic gastritis.
- For the treatment of gastric ulcer.

### Dosage and Administration
The usual adult oral dosage of SOLON is 100 mg three times per day. The dosage may be increased or decreased depending on the patient’s age and condition.

### Formulations

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Inactive ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLON Tablets 50 mg</td>
<td>Sofalcone (50 mg/tablet)</td>
<td>Anhydrous dibasic calcium phosphate, d-Mannitol, Magnesium alumonmetasilicate, Corn starch, Low substituted hydroxypropyl-cellulose, Polysorbate 80, Hypromellose, Hydrogenated oil, Magnesium stearate</td>
</tr>
<tr>
<td>SOLON Capsules 100 mg</td>
<td>Sofalcone (100 mg/capsule)</td>
<td>Anhydrous dibasic calcium phosphate, Microcrystalline cellulose, Hydroxypropylstarch, Magnesium alumonmetasilicate, Carmellose calcium, Polysorbate 80, Hypromellose, Magnesium stearate, Hydrogenated oil, Jelly, Sodium lauryl sulfate, Titanium oxide</td>
</tr>
<tr>
<td>SOLON Fine Granules 20%</td>
<td>Sofalcone (100 mg per 0.5 g powder)</td>
<td>Anhydrous dibasic calcium phosphate, d-Mannitol, Potato starch, Polysorbate 80, Hypromellose, Light anhydrous silicic acid, Flavor</td>
</tr>
</tbody>
</table>

### ID codes and Appearance, size, etc.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ID code</th>
<th>Dosage form</th>
<th>Appearance, size, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLON Tablets 50 mg</td>
<td>T290</td>
<td>Light yellow to yellow, uncoated tablet</td>
<td>Front: [Image] Back: [Image] Side: [Image] Diameter (mm): ca. 9 Thickness (mm): ca. 4.2 Weight (mg): ca. 300</td>
</tr>
<tr>
<td>SOLON Capsules 100 mg</td>
<td>T292</td>
<td>Hard capsule with white opaque body and cap</td>
<td>[Image]</td>
</tr>
<tr>
<td>SOLON Fine Granules 20%</td>
<td>T294</td>
<td>Pale yellow to light yellow, fine granules</td>
<td>[Image]</td>
</tr>
</tbody>
</table>
PRECAUTIONS
1. Adverse Reactions
A total of 23 adverse drug reactions (ADRs) were encountered in 20 (0.09%) of 22,583 patients treated with SOLON. The most common ADRs included constipation in 7 cases, thirst in 2 cases, and heartburn in 2 cases. [Results from pre- and post-approval clinical trials and post-marketing clinical experience studies.]

(1) Clinically significant adverse reactions
Hepatic dysfunction, jaundice (incidence unknown): Since hepatic function disorders with elevated liver enzyme levels etc. and/or jaundice may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as withdrawal of SOLON should be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>less than 0.1%</td>
<td>unknown</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation, thirst, heartburn</td>
<td>Rash*</td>
</tr>
</tbody>
</table>

* If any of these symptoms develop, SOLON should be discontinued.

2. Use during Pregnancy, Delivery, or Lactation
(1) The safety of SOLON during pregnancy has not been established; the drug should be administered to women known or suspected to be pregnant only if its therapeutic benefits are judged to outweigh its potential risks.

(2) Nursing mothers should discontinue breast-feeding during SOLON therapy; in rats, sofalcone has been reported to be excreted in breast milk.

3. Pediatric Use
Safety in pediatric patients has not been established; the available clinical data on the use of SOLON in pediatric patients are insufficient.

4. Precautions concerning Use
When SOLON is provided in a press-through package (PTP) sheet (a blister sheet), instruct the patient to remove a tablet/capsule from the package sheet prior to swallowing. It has been reported that, if a small part of the package is mistakenly swallowed along with a tablet/capsule, its sharp corners may penetrate and eventually perforate the esophageal mucosa, leading to serious complications (e.g., mediastinitis).

PHARMACOKINETICS
1. Absorption
Following oral administration of a single dose of 100 mg (in fine granules, tablets, or a capsule) to healthy volunteers under fasting conditions, sofalcone was rapidly absorbed from the gastrointestinal tract. The blood concentrations peaked at 0.50-0.66 μg/ml after approx. one hour and dropped to nearly zero after 12 hours. The elimination half-life was approx. one hour. No accumulation was observed with repeated administration.

2. Distribution
Animal studies: In experiments in which sofalcone was administered orally to rats, the highest concentrations were found in the liver and gastrointestinal tract. The concentrations found in other organs and tissues were comparable with or lower than those in the plasma. The levels found in the CNS were extremely low. The distribution of sofalcone was similar in normal rats and in rats with experimentally induced gastric ulcers. The long-term retention of sofalcone on the surface of the stomach was observed in both normal and ulcer-induced rats, suggesting its protective effects to be manifested through adhesion to the gastric wall.

3. Metabolism
When sofalcone was administered orally to healthy volunteers, the major metabolites were due to hydrogenation of α,β unsaturated bonds of the chalcone structure and the oxidation of isoprenyl side chains.

4. Elimination
When sofalcone was given orally to healthy volunteers, 6%-8% of the dose was excreted in the urine within 48 hours, primarily as metabolites (mainly hydrogenated derivatives of chalcone with oxidized side chains).

Animal studies:
In experiments in which sofalcone was administered orally to rats, 93% of the dose was excreted in the feces and 4% was excreted in the urine within 24 hours of dosing.

CLINICAL STUDIES
The results of open or double-blind trials involving a total of 1,120 patients are as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total efficacy rate</th>
<th>Endoscopic improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis* 7-11)</td>
<td>85.7% (335/391)</td>
<td>82.4% (322/391)</td>
</tr>
<tr>
<td>Gastric ulcer12-19)</td>
<td>82.9% (604/729)</td>
<td>78.7% (574/729)</td>
</tr>
</tbody>
</table>

* Improvement in gastric mucosal lesions (erosion, hemorrhage, redness, or edema) associated with acute gastritis or acute exacerbation of chronic gastritis

PHARMACOLOGY
1. Effect on experimental ulcers
Sofalcone prevented gastric ulceration in rats, induced by pyloric ligation, stress, reserpine, phenylbutazone, histamine or acid aspirin, and accelerated healing of acetic acid-induced gastric ulcer in rats and histamine-induced gastric ulcer in guinea pigs.

2. Effect on experimental gastritis
Sofalcone showed a therapeutic effect on chronic atrophic gastritis induced by sodium taurocholate or N-methyl-nitroso-guanidine in rats.

3. Effect on acute gastric mucosal lesions
Sofalcone prevented the formation of acute gastric mucosal lesions induced by aspirin or 50% ethanol in rats.
4. **Effect on gastric mucosal injuries**
Sofalcone inhibited gastric mucosal injuries induced by 0.6 N hydrochloric acid or 100% ethanol in rats.

5. **Increasing effect on gastric blood flow**
Sofalcone increased gastric blood flow (measured by the hydrogen gas clearance method and the cross-thermocouple method) in rats, and increased the short gastric arterial blood flow (determined by electromagnetic flowmetry) in dogs.

6. **Vasodilating effect on gastric mucosal vessels**
Sofalcone induced vasodilation in the gastric mucosal circulation in rats, observed by in situ video monitoring and by the pigment injection-transparent specimen method.

7. **Enhancement of oxygen consumption in gastric tissues**
Sofalcone increased oxygen consumption in the gastric tissues of dogs, revealed by measuring the intravascular partial pressure of oxygen.

8. **Healing effect on experimentally induced gastric ulcers**
A histological study showed that sofalcone promoted the healing of gastric mucosal lesions in acetic acid-induced ulcers in rats.

9. **Enhancement of the amount of constituents of the gastric wall**
Sofalcone enhanced enzyme activity contributing to sulfation of macromolecular glycoproteins in the rat gastric mucosa, and increased sulfated mucosubstances of the gastric wall in rats with stress-, aspirin-, or acetic acid-induced ulcer. Furthermore, sofalcone prevented reduction in the gastric mucosal macromolecular glycoprotein content and synthesis rates in rats with stress ulcers, acute gastric mucosal lesions, and sodium taurocholate-induced gastritis.

10. **Effect on adhesion to the gastric epithelium of mucus glycoproteins**
Sofalcone prevented the release of mucus glycoproteins into gastric juice and the reduction of adhesion capacity of the glycoproteins coating the gastric mucosal surfaces in 100% ethanol-treated rats.

11. **Beneficial effect on the properties of gastric mucus in vitro**
In experiments on the isolated porcine gastric mucus, sofalcone produced a marked enhancement in mucus viscosity, increased the retardation ability of mucus to hydrogen ions, and inhibited the proteolytic activity of pepsin.

12. **Inhibitory effect on production of metal proteinases**
Sofalcone suppressed the production of metal proteinases in cultured gastric cells derived from sodium taurocholate-induced gastritis in rats.

13. **Effect on proliferation of gastric mucosal cells**
Sofalcone stimulated cell proliferation (measured by ³H-thymidine incorporation in vivo) in gastric mucosa of chronic atrophic gastritis, induced in rats by treatment with sodium taurocholate.

14. **Effect on the amount of prostaglandins in gastric tissues**
In rabbits (in vitro), rats, pigs, and gastric ulcer patients, sofalcone increased the quantity of prostaglandins in the gastric mucosa. Its mechanism of action is to inhibit the prostaglandin catabolic enzyme, 15-hydroxyprostaglandin dehydrogenase (PGDH). Sofalcone also inhibited increases in PGDH activity and prevented any decrease in prostaglandin E₂ content in sodium taurocholate-induced gastritis in rats.

15. **Anti-oxidative effect**
Sofalcone prevented gastric mucosal lesions and decreased tissue levels of thiobarbituric acid-reactive substances, an indicator of lipoperoxidation, in ischemia/reperfusion-treated rats, suggesting its ability to counteract reactive oxygen species.

16. **Effect on *Helicobacter pylori***
Sofalcone showed antibacterial activity against *H. pylori*, and inhibited the adhesion of *H. pylori* to gastric mucosa in vitro.

**DESCRIPTION**

Generic name: Sofalcone

Chemical name: 2’-Carboxymethoxy-4,4’-bis(3-methyl-2-butenyloxy)chalcone

Structural formula:

Molecular formula: C₂₇H₃₇O₈

Molecular weight: 450.52

Physicochemical properties:
Sofalcone occurs as light yellow to yellow crystals or a crystalline powder. It is odorless and has no taste. It is soluble in dimethylformamide and dichloromethane; slightly soluble in methanol, 95% ethanol and 99.5% ethanol; and practically insoluble in water. It is gradually degraded by exposure to light.

Melting point: 142–146 °C

**PACKAGING**

<table>
<thead>
<tr>
<th>SOلون Tablets</th>
<th>Pack with 100 or 1000 tablets (PTP/blister pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pack with 1000 tablets (loose)</td>
</tr>
<tr>
<td>SOلون Capsules</td>
<td>Pack with 100 or 1000 capsules (PTP/blister pack)</td>
</tr>
<tr>
<td>SOلون Fine Granules</td>
<td>Pack with 100 g or 1 kg (bulk)</td>
</tr>
<tr>
<td></td>
<td>Pack with 0.5 g x 90 or 1200 (sachet pack)</td>
</tr>
</tbody>
</table>
REFERENCES

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54) Slomiany BL et al.: Digestion, 43, 33 (1989)

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