MUCOSTA Film Coated Tablet 100
(Rebamipide)

DESCRIPTION
1. Composition
   Each MUCOSTA Film Coated Tablet contains 100 mg of rebamipide.
2. Product Description
   MUCOSTA is a film-coated tablet

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Weight (mg)</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>3.4</td>
<td>Approx. 175</td>
<td>Og33</td>
<td></td>
</tr>
</tbody>
</table>

INDICATIONS
• Gastric ulcers
  In combination with offensive factor inhibitors (proton pump inhibitors, anticholinergic, H2 antagonist)
• Gastritis

CONTRAINDICATIONS
(MUCOSTA Tablets are contraindicated in the following patients)
Patient with a history of hypersensitivity to any ingredient of this drug.

DOSAGE AND ADMINISTRATION
Gastric ulcers: in combination with offensive factor inhibitors the usual adult dosage of MUCOSTA tablets is one tablet (100 mg of rebamipide) orally three times daily, in the morning, in the evening, and before bedtime.
Gastritis: The usual adult dosage of MUCOSTA Tablets is one tablet (100 mg rebamipide) orally three times daily.

PHARMACOLOGY
1. Experiment Using Animal Models
   1) Preventive of healing effects in gastric ulcer models
      Rebamipide inhibited gastric mucosal injury in various experimental rat models of ulcers, including ulcers induced by water-immersion restraint stress, acetylsalicylic acid, indomethacin, histamine, serotonin and pyloric ligation. The drug promoted healing of gastric ulcers and suppressed recurrence or relapse of ulcers even 120-140 days after ulcer production in a rat acetic acid-induced ulcer model.
   2) Preventive or healing effects in gastritis models
      Rebamipide inhibited the occurrence of taurocholic acid-induced gastritis and promoted healing of mucosal inflammation in a rat gastritis model.
3) **Prostaglandin-increasing effect**
Rebamipide increased the endogenous prostaglandin E2 (PGE2) content in the gastric mucosa in rats. The drug also increased PGE2 and PG12 content in the gastric juice, as well as the content of 15-keto-13,14-dihydro-PGE2, a metabolite of PGE2. In healthy male subjects, the drug again revealed the effect of increasing the PGE2 content in the gastric mucosa and protected the gastric mucosa from injury caused by ethanol loading.

4) **Cytoprotective effect**
Rebamipide exhibited a gastric cytoprotective effect to inhibit the mucosal injury induced by ethanol, strong acid and strong base in rats. In *in vitro* studies, the drug also protected cultured gastric epithelial cells obtained from rabbit fetuses against acetylsalicylic acid or taurocholic acid induced injury. In healthy male subjects, the drug inhibited gastric mucosal injury induced by acetylsalicylic acid, ethanol and HCl-ethanol loading.

5) **Mucus-increasing effect**
Rebamipide promoted gastric enzyme activity to synthesize high-molecular glycoproteins and increased the amounts of gastric surface mucus and soluble mucus in rats. Endogenous PGs were not involved in the increase in soluble mucus.

6) **Mucosal blood flow-increasing effect**
Rebamipide increased gastric mucosal blood flow and improved impaired hemodynamics after blood loss in rats.

7) **Activity on mucosal barrier**
Rebamipide did not ordinarily affect the gastric transmucosal potential difference in rats, but did inhibit lowering of the potential difference by ethanol.

8) **Activity on gastric alkaline secretion**
Rebamipide promoted gastric alkaline secretion in rats.

9) **Activity on mucosal cell turnover**
Rebamipide activated gastric mucosal cell proliferation and increased the number of gastric pit epithelial cells in rats.

10) **Effect on gastric mucus repair**
Rebamipide restored the bile acid- or hydrogen peroxide- induced retardation of artificial wound-repair in cultured rabbit gastric epithelial cells.

11) **Effect on gastric secretion**
Remipide did not alter either basal secretion of gastric juice or acid secretion in response to stimulation.

12) **Effects on oxygen-free radicals**
Rebamipide scavenged hydroxyl radicals directly and suppressed superoxide production by polymorphonuclear leukocytes. The drug also protected the gastric mucosal cells against injury caused by oxygen-free radicals released from neutrophils stimulated by *Helicobacter pylori in vitro*. The drug inhibited mucosal injury and reduced the content of lipid peroxide in the gastric mucosa of rats treated with indomethacin under stressed conditions.

13) **Effect on inflammatory cellular infiltration in the gastric mucosa**
Rebamipide prevented inflammatory cellular infiltration in rat models of taurocholic acid-induced gastritis, NSAID-induced gastric mucosal damage, and ischemia-perfusion-induced gastric mucosal damage.

14) **Effect on inflammatory cytokine release (interleukin-8) in the gastric mucosa**
Rebamipide suppressed the increased production and release of interleukin-8 from human gastric mucosa in the presence of \textit{Helicobacter pylori} \textit{in vitro}. The drug also inhibited the activation of NF-kB and suppressed the expression of interleukin-8 mRNA in epithelial cells in vitro.

**PHARMACOKINETICS**

1. **Plasma concentration**
   Following single oral administration at 100 mg to 12 healthy subjects, plasma concentration of rebamipide peaked (at 210 ng/mL) at 2 hours. The elimination half-life in plasma was about 1.5 hours. Repeated-administration studies have shown that the drug does not accumulate in humans. The absorption of rebamipide tended to be slow when the drug was administered orally at a dose of 150 mg to 6 healthy subjects after a meal. However, food did not affect bioavailability of the drug in humans. Pharmacokinetic parameter obtained from patients with renal impairment after single oral administration of rebamipide at 100 mg revealed higher plasma concentration and a longer elimination half-life compared with those in healthy subjects. At steady-state, rebamipide plasma concentration observed in dialyzed renal patients following repeated administration were very close to the values simulated from single administration. Therefore, the drug was not considered to accumulate.

\[ \text{Plasma concentrations of rebamipide following single oral administration at 100 mg to 12 healthy subjects.} \]

2. **Metabolism**
   Rebamipide was primarily excreted as the unchanged compound in the urine after single oral administration to healthy adult males at a dose of 600 mg. A metabolite with a hydroxyl group at the 8th position was identified in the urine. However, the excretion of this metabolite was only 0.03% of the administered dose. The enzyme involved in the formation of the metabolite was CYP3A4.
   (Note) The usual dosage in adults is 100 mg three times daily.

3. **Excretion**
   Approximately 10% of the administered dose was excreted in the urine when rebamipide was administered as a single oral dose to healthy adult males at 100 mg.

4. **Protein binding**
   Rebamipide at 0.05-5 µg/ml was added to human plasma \textit{in vitro}, and 98.4% - 98.6% of the drug was bound to plasma proteins.
CLINICAL STUDIES

1. Clinically Efficacy in Gastric Ulcer
   MUCOSTA Tablets were studied in patients with gastric ulcer, using endoscopy for objective drug evaluation. In the final endoscopic assessment, the drug achieved complete healing in 60% (200/335) of the patients studied and near-complete healing in 67% (224/335). The clinical usefulness of this drug, based on efficacy and safety was demonstrated in a double-blind study. Six months follow-up of 67 patients who showed healing at a daily dose of 300 mg revealed that that recurrence occurred in only 4 patients (approx. 6%).

2. Clinically Efficacy in Acute Gastritis and Acute Exacerbation of Chronic Gastritis
   MUCOSTA Tablets were studied in patients with acute gastritis or acute exacerbation of chronic gastritis. The drug achieved an 80% (370/461) global efficacy rate in the patient evaluated, with 76% (351/461) showing moderate or marked improvement. The drug’s clinical usefulness was found to be reproducible in a double-blind study.

PRECAUTIONS

1. Use in the Elderly
   Special care is required in elderly patients to minimize the risk of gastrointestinal disorders, because these patients may be physiologically more sensitive to this drug than younger patients.

2. Use during Pregnancy, Delivery, or Lactation
   This drug should be administered to pregnant or possibly pregnant women only if the anticipated therapeutic benefit is thought to outweigh any potential risk. (The safety of this drug in pregnant women has not been established)
   Nursing should be interrupted when this drug is administered to a nursing woman. (Rat studies have shown that rebamipide is excreted in the breast milk).

3. Pediatric Use
   The safety of this drug in children has not been established. (Clinical experience in children is insufficient.)

4. Precautions for Use
   Patient's Instruction for Use
   Patients should be instructed not ingest any portion of the press-through package (PTP). (There have been reports that the sharp edges of the sheet can cut or penetrate the esophageal mucosa if accidentally ingested, resulting in mediastinitis or other serious complications.)

ADVERSE REACTIONS

Of the 10,047 patients treated, adverse reactions, including abnormal laboratory findings, were reported in 54 patients (0.54%). Of 3,035 patients aged over 65 years, adverse reactions were noted in 18 patients (0.59%). The nature and incidence of adverse reactions were not different between the same in elderly and younger patients. The following summary of data includes adverse reactions voluntarily reported after marketing (Figures are total cases reported from the time of approval up to June 2001).

(1) Clinically significant adverse reactions
   Leukopenia (incidence < 0.1%) and thrombocytopenia (incidence unknown*):
   Leukopenia and thrombocytopenia may occur. Patient should therefore be closely monitored. If abnormal findings are observed, the drug should be discontinued and appropriate measures taken.
Hepatic dysfunction (incidence < 0.1%) and jaundice (incidence unknown*) : Hepatic dysfunction and jaundice, as indicated by increases in AST (GOT), ALT (GPT), g-GTP, and alkaline phosphatase levels, have been reported in patients receiving MUCOSTA tablets. If abnormal laboratory findings are observed, the drug should be discontinued and appropriate measures taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Body system/ Frequency</th>
<th>&lt; 0.1 %</th>
<th>*Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (note 1)</td>
<td>Rash, pruritus, drug-eruption-like eczema, and other symptoms of hypersensitivity</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Numbness, dizziness and sleepiness</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation, feeling of abdomen enlarged, diarrhea, nausea, vomiting, heartburn, abdominal pain, belching, taste abnormality, etc</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Hepatic (note 2)</td>
<td>Increased AST (GOT), ALT (GPT), g-GTP, and alkaline phosphatase levels</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Leukopenia, granulocytopenia, etc</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Other</td>
<td>Menstrual disorders, increased BUN levels, edema and feeling of a foreign body in the pharynx</td>
<td>Breast swelling and pain, gynecomastia, induction of lactation, palpitations, fever, facial flushing, numbness of tongue, cough, and respiratory distress.</td>
</tr>
</tbody>
</table>

Note 1) If such symptoms of hypersensitivity occur, the drug should be discontinued.

Note 2) If transaminase levels are markedly increased or fever and rash develop, the drug should be discontinued and appropriate measures should be taken. The incidence rates of voluntarily reported adverse reactions are not known.

**DRUG INTERACTION**

No study was done to evaluate drug interaction

**PHYSICOCHEMISTRY**

Nonproprietary name : Rebamipide (JAN)

Chemical Name :

(±)-2-(4-Chlorobenzoylamino)-3-[2(1H)-quinolinon-4-yl]propionic acid

Molecular formula :

C\(_{19}\)H\(_{15}\)ClN\(_2\)O\(_4\)

Molecular weight :

370.79
Structural formula:

Storage
Store at room temperature (25°C – 30°C)

Packaging
MUCOSTA Tablets 100
Boxes of 10 blisters of 10 film coated tablets

Manufactured by:
OTSUKA PHARMACEUTICAL CO., LTD
2-9 Kanda Tsukasa-cho, Chiyoda-ku,
Tokyo 101-8535, Japan

Imported by
PT. Otsuka Indonesia
Lawang, East Java, Indonesia