- ANTI-GASTRITIS AND ANTI-GASTRIC ULCER DRUG -

MUCOSTA® Tablets 100mg
< Rebamipide >

MUCOSTA® Granules 20%
< Rebamipide >

DESCRIPTION

1. Composition
Each MUCOSTA Tablet contains 100 mg of rebamipide.
Each MUCOSTA Granules 0.5 gram contains 100 mg of rebamipide.

2. Product Description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>MUCOSTA Tablets 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White film-coated tablets</td>
</tr>
<tr>
<td>Appearance</td>
<td>Diameter (mm)</td>
</tr>
<tr>
<td></td>
<td>8.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brand name</th>
<th>MUCOSTA Granules 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White to pale yellowish-white film-coated granules, described as either odorless or having a slight characteristic odor.</td>
</tr>
</tbody>
</table>

INDICATIONS

- Gastric ulcers
In combination with offensive factor inhibitors (Proton Pump Inhibitors, Anticholinergic, H2-antagonist).
- Gastritis

CONTRAINDICATIONS (MUCOSTA Tablets and Granules are contraindicated in the following patients)
Patients 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 rebamipide is 100 mg (1 tablet of MUCOSTA Tablets 100 mg or 0.5 g of MUCOSTA Granules 20%) taken by the oral route three times daily, in the morning, in the evening, and before bedtime.
- Gastritis: The usual adult dosage of rebamipide is 100 mg (1 tablet of MUCOSTA Tablets 100 mg or 0.5 g of MUCOSTA Granules 20%) three times daily taken by the oral route.

PHARMACOLOGY

1. Preventive or 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, aspirin, indomethacin, histamine, serotonin, and pyloric ligation. The drug also protected the mucosa from injury caused by other ulcerogenic conditions that presumably yield reactive oxygen species, including mucosal ischemia-reperfusion, administration of platelet activating factor (PAF) or diethylthiocarbamate (DDC), and administration of indomethacin under stressed conditions.
In a rat acetic acid-induced ulcer model, the drug promoted healing of gastric ulcers and was seen to suppress the recurrence and relapse of ulcers 120-140 days after ulcer induction.

2. Preventive or healing effects in gastritis models
Rebamipide inhibited the development of taurocholic acid (one of the main ingredients of bile acid)-induced gastritis and promoted healing of the mucosal inflammation associated with gastritis in rat experiments.

3. Prostaglandin-increasing effect
Rebamipide increased the generation of prostaglandin E2 (PGE2) in the gastric mucosa in rats. The drug also increased the contents of PGE2, 15-keto-13,14-dihydro-PGE2 (a metabolite of PGE2) and PGF2 in the gastric juice.
In healthy male subjects, the drug again revealed the increasing effect on 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, or strong base in rats. In in vitro studies, the drug also protected cultured gastric epithelial cells obtained from rabbit fetuses against aspirin- or taurocholic acid (one of the main ingredients of bile acid)-induced injury.
In healthy male subjects, the drug inhibited gastric mucosal injury induced by aspirin, ethanol, or HCl-ethanol loading.

5. Mucus-increasing effect
Rebamipide promoted gastric enzyme activity to synthesize high molecular weight glycoproteins, thickened the superficial mucous layer of gastric mucosa, and increased the amount of gastric 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. Effect 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. Effect on gastric alkaline secretion
Rebamipide promoted gastric alkaline secretion in rats.
9. **Effect on mucosal cell turnover**
   Rebamipide activated gastric mucosal cell proliferation and increased the number of covering epithelial cells in rats.

10. **Effect on gastric mucosal 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**
    Rebamipide did not alter either basal secretion of gastric juice or secretagogue-stimulated acid secretion.

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

13. **Effect on inflammatory cell infiltration in the gastric mucosa**
    Rebamipide prevented inflammatory cell infiltration in rat models of taurocholic acid (one of the main ingredients of bile acid)-induced gastritis and NSAID-induced or ischemia-reperfusion-induced gastric mucosal damage.

14. **Effect on inflammatory cytokine release (Interleukin-8)**
    in the gastric mucosa
    Rebamipide, taken by the oral route, suppressed the increased production of interleukin-8 in the mucosa of patients with *Helicobacter pylori*. The drug also inhibited activation of NF-κB, the expression of interleukin-8 mRNA, and the production of interleukin-8 in epithelial cells cocultured with *Helicobacter pylori*.

**PHARMACOKINETICS**

1. **Plasma Concentrations**
   The table below shows the pharmacokinetic parameters of rebamipide following single oral administration of MUCOSTA Tablets 100 mg or MUCOSTA Granules 20% at a dose of 100 mg to 27 healthy male subjects in a fasted state. MUCOSTA Tablets and MUCOSTA Granules are bioequivalent. Repeated administration studies have shown that the drug does not accumulate in humans.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters of Rebamipide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>MUCOSTA Tablets 100 mg</td>
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<tr>
<td>MUCOSTA Granules 20%</td>
</tr>
</tbody>
</table>

Mean values±SD, n=27, t1/2 calculated from values up to 12 hr

The absorption rate of rebamipide following single oral administration at a dose of 150 mg to 6 healthy male subjects in a fed state tended to be slower than that in a fasted state. However, food did not affect bioavailability of the drug in humans. Pharmacokinetic parameters obtained from patients with renal impairment after single oral administration of rebamipide at 100 mg revealed higher plasma concentrations and a longer elimination half-life compared with those in healthy subjects. At steady-state, rebamipide plasma concentrations 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.

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 in vitro, and 98.4% - 98.6% of the drug was bound to plasma proteins.

**CLINICAL STUDIES**

1. **Clinical 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 69% (200/303) 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-month follow-up of 67 patients who showed healing at a daily dose of 300 mg revealed that recurrence occurred in only 4 patients (approx. 6%).

2. **Clinical 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 patients 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
(1) 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.)
(2) Nursing should be interrupted when this drug is administered to. (Rat studies have shown that rebamipide is excreted in the breast milk.)

3. Pediatric Use
The safety of this drug in low birth weight infants, newborns, sucking infants, infants and children has not been established. (Clinical experience is insufficient.)

4. Precautions for Use
MUCOSTA Tablets 100 mg

Patient's Instructions for Use:
Patients should be instructed not to 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 10,047 patients treated, adverse reactions, including abnormal laboratory findings, were reported in 64 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 showed no differences between elderly and younger patients. The following summary of data includes adverse reactions voluntarily reported after marketing (Figures are total cases reported at the time of approval and at the completion of reexamination of MUCOSTA Tablets 100).

(1) Clinically significant adverse reactions
1) Shock, anaphylactoid reactions (incidence unknown*): Shock or anaphylactoid reactions may occur. Patients should therefore be closely monitored. If abnormal findings are observed, the drug should be discontinued and appropriate measures taken.
2) 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.
3) Hepatic dysfunction (incidence <0.1%) and jaundice (incidence unknown*): Hepatic dysfunction and jaundice, as indicated by increases in AST (GOT), ALT (GPT), γ-GTP, and alkaline phosphatase levels, have been reported in patients receiving MUCOSTA Tablets or MUCOSTA Granules. Patient should therefore be closely monitored. 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>Hyper-sensitivity (note 1)</td>
<td>Rash, drug-eruption-like eczema, other symptoms of hypersensitivity</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Neuro-psychiatric</td>
<td>Numberless, dizziness, sleepiness</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</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*</td>
<td>Increased AST (GOT), ALT (GPT), γ-GTP, alkaline phosphatase levels</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>Leukopenia, granulocytopenia, thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Menstrual disorders, increased BUN levels, edema, 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, respiratory distress, alopecia</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:
(2RS)-2-(4-Chlorobenzylationamo)-3-(2-oxo-1,2-dihydroquinolin-4-yl) propionic acid
Structural formula:

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{O} & \quad \text{O} \\
\text{CoH} & \quad \text{Cl} \\
\text{and enantiomer} & \quad
\end{align*}
\]
Molecular formula:
C_{16}H_{23}ClN_{2}O_{4}
Molecular weight: 
370.79

Description:
Rebamipide occurs as a white crystalline powder. It has a
bitter taste. It is soluble in N,N-dimethylformamide, very
slightly soluble in methanol and ethanol (99.5), and practically
insoluble in water. Its N,N-dimethylformamide solution
(1→20) shows no optical rotation.
Melting point: About 291°C (decomposition)

STORAGE
Store below 30 °C

PACKAGING
MUCOSTA Tablets 100 mg:
Boxes of 10 blister of 10 tablets
REG No DKL0518707017A1

MUCOSTA Granules 20%:
Boxes of 5 X 3 sachets containing 0.5 g of
MUCOSTA Granules 20%
REG No DKLxxxxxxxx

HARUS DENGAN RESEP DOKTER

MUCOSTA TABLET
Manufactured by:
PT Otsuka Indonesia
Jl Sumber Waras No 25
Lawang, Malang 65216, Indonesia

MUCOSTA GRANULA 20%
Manufactured and primary packaging by:
Chosido Pharmaceutical Co., Ltd.
92 Ko, Kokufu-Cho,
Tokushima 779-3122, Japan

Batch release by
Otsuka Pharmaceutical Co., Ltd.
463-10, Kasaijima, Kawashimi-cho,
Tokushima 771-0192, Japan

Imported by:
PT Otsuka Indonesia
Jl Sumber Waras No 25
Lawang, Malang 65216, Indonesia