Name
MUCOSTA Tablets 100

Description
1. Composition
MUCOSTA Tablets 100:
Each MUCOSTA Tablet contains: 100mg of rebamipide and the following inactive ingredients: crystalline cellulose, hydroxypropylcellulose, magnesium stearate, hydroxy propylmethylcellulose, Macrogol 6000, and titanium oxide.

2. Product Description
MUCOSTA Tablets 100 are white film-coated tablets.
Appearance: a small white circular pill with OG33 imprinted on one side and a blank side.
Diameter: 8.1 mm
Thickness: 3.4 mm
Weight: Approx. 175 mg
Code: OG33

Indications
Anti-gastritis and Anti-gastric Ulcer Drug

Gastric ulcers

Treatment of gastric mucosal lesions (erosion, bleeding, redness, and edema) in the following conditions; acute gastritis and acute exacerbation of chronic gastritis.

Dosage and Administration
Gastric ulcers: The usual adult dosage of rebamipide is 100 mg (1 MUCOSTA Tablet) taken by the oral route three times daily, in the morning, in the evening, and at bedtime.

Treatment of gastric mucosal lesions (erosion, bleeding, redness, and edema) in the following conditions; acute gastritis and acute exacerbation of chronic gastritis: The usual adult dosage of rebamipide is 100 mg (1 MUCOSTA Tablet) three times daily taken by the oral route.

Precautions
1. Adverse Reactions:

Of 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 at the time of approval and at the completion of reexamination of MUCOSTA Tablets 100).

(1) Clinically significant adverse reactions
1) 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.

2) Hepatic dysfunction (incidence < 0.1%) and jaundice (incidence unknown*): Hepatic dysfunction and jaundice, as indicated by increases in AST (GOT), ALT (GPT), gamma-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

Hypersensitivity (note 1):
- < 0.1%: Rash, pruritus, drug-eruption-like eczema, and other symptoms of hypersensitivity
- *Incidence unknown: Urticaria

Neuropsychiatric:
- < 0.1%: ----- 
- *Incidence unknown: Numbness, dizziness, and sleepiness

Gastrointestinal:
- < 0.1%: Constipation, feeling of abdomen enlarged, diarrhea, nausea, vomiting, heartburn, abdominal pain, belching, taste abnormality, etc.
- *Incidence unknown: Dry mouth

Hepatic (note 2):
- < 0.1%: Increased AST (GOT), ALT (GPT), gamma-GTP, and alkaline phosphatase levels
- *Incidence unknown: ----- 

Hematologic:
- < 0.1%: Leukopenia, granulocytopenia. etc.
- *Incidence unknown: Thrombocytopenia

Other:
- < 0.1%: Menstrual disorders, increased BUN levels, edema, and feeling of a foreign body in the pharynx
- *Incidence unknown: Breast swelling and pain, gynecomastia, induction of lactation, palpitations, fever, facial flushing, numbness of tongue, cough, respiratory distress, and alopecia

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.

2. 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.

3. 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 a nursing woman. (Rat studies have shown that rebamipide is excreted in the breast milk in nursing rats.)

4. Pediatric Use:-

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

5. Precautions for Use:-

Patients 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.)

Pharmacokinetics
1. Plasma Concentrations:-

Following single oral administration at 100 mg to 27 healthy subjects, plasma concentrations of rebamipide peaked (at 216 ng/mL) at 2.4 hours. The elimination half-life in plasma was about 1.9 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 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.

Pharmacokinetic Parameters of Rebamipide
MUCOSTA Tablets 100
tmax: 2.41.2 (hr)
Cmax: 21679 (ng/mL)
t: 1.90.7 (hr)
AUC (24h): 874209 (ng hr/mL)

Mean value  SD, n=27, t calculated from values up to 12 hr

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 g/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 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-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.

Pharmacology

1. Experiments Using Animal Models:

(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 oxygen free-radicals, including mucosal ischemia-reperfusion, administration of platelet activating factor (PAF) or diethyldithiocarbamate (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-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 PGI2 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-induced injury. In healthy male subjects, the drug inhibited gastric mucosal injury induced by aspirin, ethanol, or HC1-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 oxygen free-radicals:
Rebamipide scavenged hydroxyl radicals directly and suppressed superoxide production by polymorphonuclear leukocytes. The drug inhibited the gastric mucosal cell injury caused by oxygen free-radicals 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-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 the activation of NF-kB, the expression of interleukin-8 mRNA, and the production of interleukin-8 in epithelial cells cocultured with Helicobacter pylori.

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

Physicochemistry
Non-proprietary name:
rebamipide (JAN)

Chemical name:
(\text{()-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

Packaging
MUCOSTA Tablets 100:
Boxes of 20 tablets in two blisters each of 10 tablets.

Storage
Store at room temperature (below 30°C).

Expiration Date
Three years after the date of manufacturing
(The expiration date is indicated on the package.)

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