8.26 x 8.2in (210 x 310 mm)

	MUCOSTA Tablets 100 mg
Registration No.	DRP - 6291
Date of revision of Package Insert	April 2022
Date of First Authorization	December 2002

Otsuka

Manufactured by:
KOREA OTSUKA PHARMACEUTICAL CO., LTD.
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Otsuka

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Sun Valley, Parañaque City

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Rebamipide

Mucosta®
100mg Tablet

DESCRIPTION Mucosal Protectant

1. **Composition**
   Each **Rebamipide (Mucosta)® tablet** contains 100mg of rebamipide.
2. **Product Description**
   Rebamipide (Mucosta)® tablet 100mg is a white, film - coated tablet.

Appearance	Diameter (mm)	Thickness (mm)	Weight (mg)	Code
	8.1	3.4	Approx 175	OG33

INDICATIONS

1. Indicated for the treatment of gastric mucosal lesions (erosion, bleeding, redness, and edema) in the following conditions: acute gastritis and acute exacerbation of chronic gastritis.
2. Indicated for gastric ulcer.
3. Indicated for NSAID – induced gastropathy and enteropathy.

DOSAGE AND ADMINISTRATION

1. In the 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 is one tablet (100mg) orally three times daily.
2. Gastric ulcers: The usual adult dosage is one tablet (100mg) orally three times daily, in the morning, in the evening, and before bed.
3. NSAID-induced gastropathy and enteropathy: The usual dosage is one tablet (100mg of rebamipide) orally three times daily.

CONTRAINDICATIONS

Rebamipide (Mucosta)® tablets are contraindicated in the following patients:
Patients with a history of hypersensitivity to any ingredient of this drug.

PRECAUTIONS

1. **Adverse Reactions**
   Of **10,047 patient**s 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 elderly and younger patients. The following summary of date includes adverse reactions voluntarily reported after marketing (Figures ar total cases reported from the time of approval up to June 2001).

(1) Clinically siginificant 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**. 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

Body System/Frequency	<0.1%	*Incidence unknown
Hypersensitivity (note 1)	Rash, pruritus, drug-eruption-like eczema, other symptoms of hypersensitivity	Urticaria
Neuropsychiatric		Numbness, dizziness, sleepiness
Gastrointestinal	Constipation, feeling of abdomen enlarged, diarrhea, nausea, vomiting, heartburn, abdominal pain, belching, taste abnormality, etc.	Thirst
Hepatic (note 2)	Increased AST (GOT), ALT (GPT), γ-GTP, alkaline phospatase levels	
Hematologic	Leukopenia, granulocytopenia, etc.	Thrombocytopenia
Other	Menstrual disorders, increased BUN levels, edema, feeling of a foreign body in the pharynx	Breast swelling and pain, gynecomastia, induce lactation, palpitations, fever, facial flushing, numbness of tongue, cough, respiratory distress, 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 should be given to 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 used on 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 showed Rebamipide is distributed in the breast milk.)
4. **Pediatric Use**
   The safety of this drug in children has not been established (clinical experience in children is insufficient).

TOXICITY

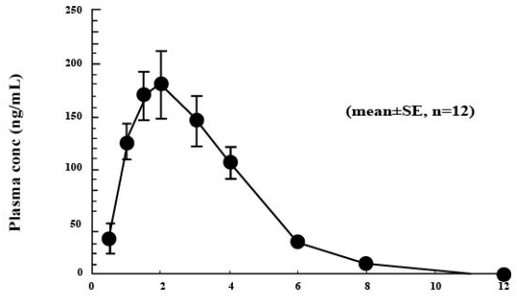
Reproductive and Development Toxicity

Reproductive and developmental toxicity studies of rebamipide were conducted using SD Rats treated prior to and in the early gestational period at 30-1,000 mg/kg/day. SD rats and NZW rabbits treated during the organogenic at 30-1,000 mg/kg/day, respectively, and SD rates treated during the perinatal and lactational periods at 10-1,000 mg/kg/day. The drug exhibited no toxic effects in either parent of F1 offspring in these species.

PHARMACOKINETICS

1. **Plasma Concentrations**

   Following single oral administration at 100 mg to 12 healthy individual, plasma concentrations of rebamipide reached the peak level (at 210ng/mL) in 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 150mg to 6 healthy individual subjects after meal. However, food did not affect the bioavailability of the drug in human. Pharmacokinetic parameters obtained from the patients with the 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 concentations observed in dialyzed renal patients following repeated administration were very close to the values simulated from single adminisration. Therefore, the drug was not considered to accumulate.



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 a single oral administration to healthy adult males at a dose of 600 mg. A metabolite with a hydroxyl group at the 8th position was unidentified 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 CYP3A.

   (Note) The usual dosage in adults is 100 mg three times daily.

3. **Excretion**

   Approximately 10% of the administered dosed was excreted in the urine when rebamipide was administered once orally to healthy adult males at 100mg.

4. **Protein Binding**

   Rebamipide at 0.05 - 5 mcg/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**

   Rebamipide (Mucosta®) tablets were studied in patients with gastric ulcers, using endoscopy for objective drug evaluation. In the final endoscopic assessment, the drug achieved complete healing rate in 60% (200/335) of the patients studied and near-complete healing in 67% (224/335). Clinical usefulness of this drug, based on efficacy and safety were demonstrated in a double-blind study 6 month follow-up of 67 patients who showed healing at a daily dose of 300 mg revealed that recurrence in only 4 patients (approx. 6%).

2. **Clinical Efficacy in Acute Gastritis and Acute Exacerbation of Chronic Gastritis**

   Rebamipide (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 patients evaluated, with 76% (351/461) showing moderate or marked improvement. The drug's clinical usefulness can be reproduced in a double-blind study.

PHARMACOLOGY

1. **Experiments Using Animal Models**

   (1) Preventive or healing effects in gastric ulcer models

   Rebamipide inhibited gastric mucosal damage in various experimental rat models of ulcers, including ulcers induced by water immersion retraint stress, aspirin, indomethacin, histamine, serotonin, and pyloric ligation. The drug also protected the mucosa from damage caused by other ulcerogenic agents that presumably yield oxygen-free radicals, including mucosal ischemia and reperfusion, administration of platelet activating factor (PAF) or diethyldithio-carbamate (DDC), and administration of indomethacin under stress conditions. 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 gastric models

   Rebamipide inhibited the occurence of taurocholic acid-induced gastritis and promoted healing of mucosal infalmmation in a rat gastritis model.

2. **Mechanism of Action**

   (1) Prostaglandin-increasing effect

   Rebamipide increased the endogenous prostaglandin E2 (PGE2) 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.

   (1) Cytoprotective effect

   Rebamipide exhibited a gastric cytoprotective effect by inhibiting mucosal damage induced by ethanol, strong acid, and strong base in rat experiments. The drug protected gastric epithelial cells *in vitro* against aspirin or taurocholic acid-induced injury in cultured cells obtained from rabbit's fetuses. In healthy male subjects, the drug inhibited gastric mucosal injury induced by aspirin, ethanol, and HCl-ethanol loading.

   (3) Mucus-increasing effect

   Rebamipide promoted enzyme activity to synthesize high molecular glycoproteins and increased the amounts of gastric surface mucus and soluble mucus in rats. Endogenous PGs are not involved in the increase in soluble mucus.

   (4) Mucosal blood flow-increasing effect

   Rebamipide increased gastric mucosal blood flow and improved hemodynamics after blood loss in rats.

   (5) Activity on mucosal barrier

   Rebamipide did not ordinarily affect the gastric transmucosal potential difference in rats, but did inhibit a decrease in the potential difference by ethanol in the stomach of rats.

   (6) Activity on gastric alkaline secretion

   Rebamipide promotes alkaline secretion in the stomach of rats.

   (7) Activity on mucosal cell turn over

   Rebamipide activated gastric mucosal cell proliferation and increased the number of epithelial cells in the stomach of rats.

   (8) Effect on gastric mucous repair

   Rebamipide restored the bile acid or hydrogen peroxide-induced retardation of artificial wound repair in cultured rabbit gastric epithelial cells.

   (9) Effect on gastric secretion

   Rebamipide did not alter either basal secretion of gastric juice or stimulatory acid secretion.

   (10) Effects on oxygen-free radicals

   Rebamipide scavenged hydroxyl radicals and suppressed superoxide production by polymophonuclear leukocytes. The drug also protected the gastric mucosa from damage by oxygen-free radical released from neutrophils stimulated by *Helicobacter pylori in vitro*. The drug inhibited mucosal damage and reduced the content of lipid peroxide in the gastric mucosa of rats treated with indomethacin under stressed conditions.

   (11) 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.

   (12) Effect on inflammatory cytokine release (interleukin-8) in the gastric mucosa

   Rebamipide suppressed the increased production and release of interleukin-8 from human gastric muscosa in the presence of *Helicobacter pylori in vitro*. The drug also inhibited the activation of NF-KB and suppressed the expression of interleukin-8 mRNA in epithelial cells *in vitro*.

PHYSICOCHEMISTRY

Nonpropriety name:

Rebamipide (JAN)

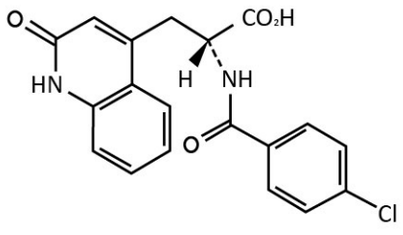
Chemical name:

(2RS)-2-(4-Cholorobenzoylamino)-3-(2-oxo-1, 2-dihydroquinolin-4-yl) propionic acid

Molecular formula:

$C_{19}H_{15}ClN_2O_4$

Structural formula:



and enantiomer

FDA Registration No. DRP-6291

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

Caution:

Foods, Drugs, Devices and Cosmetics Act prohibit dispensing without prescription.

Storage:

Store at temperatures not exceeding 30°C.

PACKAGING:

MUCOSTA Tablets 100 mg: 100 tablets in PTP