- ANTI-GASTRITIS AND ANTI-GASTRIC ULCER DRUG –

MUCOSTA® Tablets 100mg

< Rebamipide >

DESCRIPTION

1. Composition

Each MUCOSTA Tablet contains 100 mg of rebamipide.

2. Product Description

Brand name	**MUCOSTA Tablets 100 mg**			
Description	White film-coated tablets			
Appearance	**Diameter (mm)**	**Thickness (mm)**	**Weight (mg)**	**Code**
	8.1	3.4	Approx 175	OG 33

INDICATIONS

- Gastric ulcers
  In combination with offensive factor inhibitors (Proton Pump Inhibitors, Anticholinergic, H_2-antagonist).
- Gastritis

CONTRAINDICATIONS (MUCOSTA Tablets 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**) taken by the oral route three times daily, in the morning, in the evening, and before at bedtime.
- Gastritis: The usual adult dosage of rebamipide is 100 mg (1 tablet of **MUCOSTA Tablets 100 mg**) 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 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 (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 E_2 (PGE_2) in the gastric mucosa in rats. The drug also increased the contents of PGE_2, 15-keto-13,14-dihydro-PGE_2 (a metabolite of PGE_2) and PGI_2 in the gastric juice.

In healthy male subjects, the drug again revealed the increasing effect on the PGE_2 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.

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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 the 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** at a dose of 100 mg to 27 healthy male subjects in a fasted state. Repeated administration studies have shown that the drug does not accumulate in humans.

Pharmacokinetic Parameters of Rebamipide

	t_{max} (hr)	C_{max} (μg/L)	$t_{1/2}$ (hr)	AUC_{24h} (μg/L·hr)
MUCOSTA Tablets 100 mg	2.4±1.2	216±79	1.9±0.7	874±209

Mean value±SD, n=27, $t_{1/2}$ 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 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.

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, suckling 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 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 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**. 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
Hyper-sensitivity (note 1)	Rash, pruritus, drug-eruption-like eczema, other symptoms of hypersensitivity	Urticaria
Neuro-psychiatric		Numbness, dizziness, sleepiness
Gastro-intestinal	Constipation, feeling of abdomen enlarged, diarrhea, nausea, vomiting, heartburn, abdominal pain, belching, taste abnormality, etc.	Dry mouth
Hepatic(note 2)	Increased AST (GOT), ALT (GPT), γ-GTP, alkaline phosphatase 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, induction of 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.

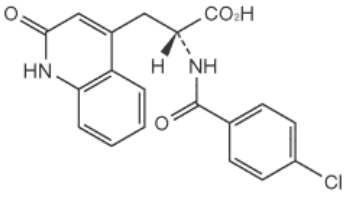
*The incidence rates of voluntarily reported adverse reactions are not known.

DRUG INTERACTION

No study was done to evaluate drug interaction.

PHYSICOCHEMISTRY

Nonproprietary name:
Rebamipide (JAN)
Chemical name:
(2*RS*)-2-(4-Chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl) propionic acid
Structural formula:



and enantiomer

Molecular formula:
$C_{19}H_{15}ClN_2O_4$
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

SHELF LIFE

Mucosta tablet 100 mg : 36 months

PACKAGING

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

HARUS DENGAN RESEP DOKTER

MUCOSTA TABLET

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

Under License of:
Otsuka Pharmaceutical Co., Ltd., Japan

DISETUJUI OLEH BPOM : 06/04/2021 ID REG : EREG100214VR12100019