Costareb tablet 100 mg

Description

- **Composition**

Each costareb tablet contains 100 mg of rebamipide and the following inactive ingredients: Microcrystalline Cellulose , Sodium Starch Glycolate , Crospovidone XL type A, Povidone K30, Colloidal silicon dioxide , Magnesium stearate , Hydroxypropyl methylcellulose (HMPC E5), Titanium dioxide , Talc , Polyethylene glycol (PEG 6000).

Indications

- 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 Costareb tablet) taken by oral route three times daily, in the morning, in the evening, 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 Costareb tablet) three times daily taken by oral route.

Precautions

1- Adverse reactions

Adverse reactions, including abnormal laboratory findings, were reported as (0.54%). In patients aged 65 years, adverse reactions were noted as (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 .

(1) Clinically significant adverse reactions

1) **Leucopenia (incidence <0.1%) and thrombocytopenia (Incidence unknown*):** Leucopenia 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), 8-GTP, and alkaline phosphatase levels, have been reported in patient receiving Rebamipide tablets. 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 unkown**
Hypersensitivity (note 1)	Rash, pruritus, drug-eruption-like eczema, and other symptoms of hypersensitivity	Urticaria
Neuropsychiatric		Numbness, dizziness, and sleepiness
Gastrointestinal	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), 8-GTP, and alkaline phosphatase levels	

Hematologic	Leukopenia, granulocytopenia, etc.	Thrombocytopenia
Other	Menstrual disorders, increased BUN levels, edema, and 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, 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 or 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 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 been established)
(2) Nursing should be interrupted when this drug is administered to nursing woman.

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

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.)

PHARMACOKINETICS

1-Plasma Concentrations

Following single oral administration at 100 mg to 27 healthy subjects, plasma concentrations of rebamipide peaked (at 216ng/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 show when the drug was administration orally at a dose of 150 mg to 6 healthy subjects after a meal.
However. Food did not affect bioavailability of the drug in the 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 concentration observed in dialyzed renal patient following repeated administration were very close to the values simulated from single administration.

Therefore, the drug was not considered to accumulate.

Pharmacokinetics Parameters of Rebamipide

	tmax (hr)	**Cmax (ng/ml)**	**t1/2 (hr)**	**AUC24h (ng hr/mL)**
Rebamipide 100 mg tablet	2.4±1.2	216±79	1.9±0.7	874±209

Mean value ± SD, n=27, t1/2 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 the 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-Protine Binding

Rebamipide at 0.05-5μg/mL was added to human plasma *in vitro*, and 98.4% - 98.6% of the drug was bound to plasma proteins.

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.

(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 prostaglandin E2, a metabolite of PGE2 and PGI2 in the gastric juice.

(4) Cytoprotective effect

Rebamipide exhibited a gastric cytoprotective effect to inhibit the mucosal injury induced by ethanol, strong acid, or strong base in rats.

(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 ordinarly affect the gastric transmucosal potential difference in rats, but did inhibit lowering of the 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 rat.

(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-κB, the expression of interleukin-8mRNA,and the production of interleukin-8 in epithelial cells cocultured with *Helicobacter pylori.*

Contraindications

Costareb tablets are contraindicated in the following patients:

Patients with a history of hypersensitivity to any ingredient of this drug.

Storage condition

Store at temperature not exceeding 30 ° C in dry place.

Pack:

Carton box contains 3 (AL/PVDC) blisters each contains 10 film coated tablets and inner leaflets.

Manufactured by: Averroes Pharma for pharmaceutical industries
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