TOWA PHARMACEUTICAL CO., LTD.

Revised: November 2014 (12th version, Drug Interactions section, etc.)
Revised: September 2013

Therapeutic Agent for Peptic Ulcer and Gastritis

MAAREDGE COMBINATION-DS FOR SUSPENSION

Storage:
Store at room temperature (avoiding moisture after opening the package).

Expiration date:
Indicated on the package.

Standard Commodity Classification No. of Japan 872349	
Approval No.	22100AMX01297
Date of listing in the NHI reimbursement price	September 2009
Date of initial marketing in Japan	July 1998

CONTRAINDICATIONS (MAAREDGE Oral Dry Susp. is contraindicated in the following patients.)

Patients undergoing hemodialysis [Aluminum encephalopathy, aluminum osteodystrophy and anaemia may occur due to a long-term administration.]

DESCRIPTION

Active ingredient in 1 gram	Dried Aluminum Hydroxide Gel (JP) ····· 448 mg (As aluminum oxide 224 mg) Magnesium Hydroxide ····· 400 mg	
Inactive ingredients	D-Mannitol, Microcrystalline Cellulose, Saccharin Sodium, Light Anhydrous Silicic Acid	
Dosage form and appearance	White granules. They are odorless and have a slightly sweet taste. They are dose-unit packages of 1.2g/pack.	
Identification code	Packaging	Tw609 (Indicated on the package)

INDICATIONS

Antacid effects and improvement of symptoms in the following diseases

Gastroduodenal ulcer, gastritis, abnormality of upper gastrointestinal tract function

DOSAGE AND ADMINISTRATION

Usually for adults, 1.6 to 4.8 g/day of this product is divided into several times and 1 g is suspended into 10 mL of water before use to be orally administered, or this product is orally administered without change. The dosage may be adjusted according to the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration (MAAREDGE Oral Dry Susp. should be administered with care in the following patients.)

1) Patients with renal dysfunction [Aluminum encephalopathy, aluminum osteodystrophy and anaemia due to a long-term administration and hypermagnesemia may occur. Blood magnesium, aluminum, phosphorus, calcium, alkaline phosphatase, etc. should be regularly measured.]
2) Patients with cardiac function failure [Magnesium has the inhibitory effect of cardiac function.]
3) Patients with diarrhea [Diarrhea may be promoted due to laxative property of magnesium hydroxide.]
4) Patients with hypermagnesemia [Blood concentration of magnesium may be increased.]
5) Patients with phosphate decreased [Aluminum inhibits the absorption of inorganic phosphorus.]

2. Drug Interactions

Precautions for coadministration (MAAREDGE Oral Dry Susp. should be administered with care when coadministered with the following drugs.)

Adsorption effects of this product or increased pH within the gastrointestinal tract and of body fluid may affect absorption and excretion of coadministered drugs. Therefore, this product should be administered with care.

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Penicillamine	Effects of penicillamine may be reduced.	It has been reported that absorption ratio of penicillamine is decreased when this product is administered together with penicillamine.
Mycophenolate mofetil	Effects of mycophenolate mofetil may be reduced.	It has been reported that absorption of mycophenolate mofetil is decreased when this product is coadministered with mycophenolate mofetil.
Azithromycin hydrate	It has been reported that maximum blood concentration of azithromycin hydrate is decreased.	The mechanism is not known.
Tetracyclines antibiotics Tetracycline Minocycline, etc.	Effects of these coadministered drugs may be reduced. This product should be administered with care such as not administering these drugs at the same time.	It is considered that chelate is formed and absorption of these drugs is inhibited.
New quinolone antimicrobial agents Enoxacin hydrate Ciprofloxacin Norfloxacin, etc.		
Bisphosphonate bone metabolism improving agent Etidronate disodium		
Digitalis preparations Digoxin, etc.		It is considered that absorption of these drugs is inhibited due to adsorption to this product in the gastrointestinal tract.
Thyroid hormone preparations Levothyroxine sodium hydrate, etc.		
Bile acid preparations Ursodeoxycholic acid Chenodeoxycholic acid		
Fexofenadine		
Iron preparations Ferrous sulfate Ferrous fumarate		It has been reported that absorption of these drugs is inhibited due to increased gastric pH and formation of insoluble salt resulting from this product.
Cefdinir Cefpodoxime Proxetil		The mechanism is not known. However, it is considered that absorption of these drugs is inhibited.
Active vitamin D_3 preparations α-calcidol Calcitriol	Hypermagnesemia may occur. This product should be administered with care.	Absorption of magnesium from the intestinal tract is considered to be promoted due to these drugs. (Especially patients with renal dysfunction)
Citric acid preparations Potassium citrate Sodium citrate	Blood concentration of aluminum may be increased. This product should be administered	It is considered that chelate is formed and absorption of aluminum is promoted.

	with care such as not administering these drugs at the same time.	
Serum potassium inhibiting ion-exchange resins Calcium polystyrene sulfonate Sodium polystyrene sulfonate	Alkalosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of this product should be taken.	It is considered that metal cation of this product and ion-exchange resins are bound and bicarbonate secreted in the intestinal tract is reabsorbed without being neutralized.
Massive milk Calcium preparations	Milk-alkali syndrome (hypercalcemia, azotaemia, alkalosis, etc.) may occur. Patients should be carefully monitored, and if such symptoms are observed, administration of this product should be discontinued.	The mechanism is not known. However, increased serum calcium and increased pH due to this product are considered to be involved.
Dolutegravir sodium	This product decreases the plasma concentration of Cmax of dolutegravir by 72% and C_{24} by 74%. The administration of dolutegravir sodium is recommended at 2 hours before or 6 hours after the administration of this product.	The absorption of dolutegravir is inhibited due to the formation of complexes.

3. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

	*Incidence unknown
Hypersensitivity	Itching, urticarias, angioedemas
Gastrointestinal	Anorexia, nausea, stomach discomfort, constipation, diarrhea, etc.
Abnormal metabolism*	Hypermagnesemia, hepophosphataemia and rickets/osteomalacia/hypercalciuria associated with it
Long-term administration*	Aluminum encephalopathy, aluminum osteodystrophy, anaemia

*: These symptoms may occur due to a long-term or massive administration. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken such as reduction of dosage or discontinuation of this product.

4. Use in the Elderly

Since adverse reactions are likely to occur in elderly patients, attention should be paid. [Elderly patients often have reduced physiological functions.]

5. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants and children has not been established. (There is no sufficient clinical data in pediatric patients.)

6. Overdose

Symptoms: A predicted symptom in usual patients is diarrhea, abdominal pain, vomiting etc. but overdose may cause hypermagnesemia in patients with renal dysfunction.

Treatment: In case of massive overdose, appropriate measure should be taken such as gastric lavage and administration of a cathartic not containing magnesium.

7. Precautions Concerning Use

Precautions during oral administration: This product should be suspended before use and immediately taken after suspension. When this product is orally administered with water, it should be taken with a cup of water.

PHARMACOLOGY

Pharmacodynamic studies

MAAREDGE COMBINATION-DS FOR SUSPENSION and a reference drug (as 1.42 g/kg body weight of preparation) were orally administered to three experimental ulcer rat models (hydrochloric acid – ethanol gastric mucosa lesion model, pylorus ligation – aspirin gastric ulcer model, and mepirizole duodenal ulcer model). From the results, both drugs showed significant inhibitory effects to gastric mucosa lesion, gastric mucosa ulcer, and duodenal ulcer, and were considered to be equivalent[1].

PHYSICOCHEMISTRY

1. Dried Aluminum Hydroxide Gel

Nonproprietary name: Dried Aluminum Hydroxide Gel

Description: Dried Aluminum Hydroxide Gel occurs as a white, amorphous powder. It is odorless and tasteless. It is practically insoluble in water, in ethanol (95) and in diethyl ether. Most of it dissolves in dilute hydrochloric acid and in sodium hydroxide TS.

2. Magnesium Hydroxide

Nonproprietary name: Magnesium Hydroxide

Molecular formula: $Mg(OH)_2$

Molecular weight: 58.32

Description: Magnesium Hydroxide occurs as a white, odorless powder. It is practically insoluble in water and in ethanol. It dissolves in dilute hydrochloric acid.

PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), MAAREDGE COMBINATION-DS FOR SUSPENSION was estimated to be stable for 3 years under normal distribution conditions[2].

PACKAGING

MAAREDGE COMBINATION-DS FOR SUSPENSION:
1.2g x 1,200 packages

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Pharmacodynamic studies
2) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

CONTACT INFORMATION ON REQUEST FOR LITERATURE AND PRODUCT INFORMATION

Please request references (including internal data) to the following address.

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