Revised: June 2013 (4th version, Change of trade name)
Revised: April 2010 (3rd version)

Calcium Aspartate Preparation

CALCIUM L-ASPARTATE TABLETS 200mg "TOWA"

Storage:
Store at room temperature.
Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 873214	
Approval No.	22500AMX00420
Date of listing in the NHI reimbursement price	June 2013
Date of initial marketing in Japan	July 2006

CONTRAINDICATIONS (Calcium L-Asparate is contraindicated in the following patients.)

1) Patients with hypercalcemia [Hypercalcemia may be aggravated.]
2) Patients with renal calculus [Renal calculus may increase in number and size.]
3) Patients with serious renal failure [Hypercalcemia may occur due to decreased calcium excretion in such patients.]

DESCRIPTION

Active ingredient per tablet	Calcium L-Aspartate Hydrate (as an anhydrate) ····· 200mg (Ca^{24}: 1.3mEq)		
Inactive ingredient	Corn Starch, Pregelatinized Starch, Sodium Starch Glycolate, Magnesium Stearate		
Product description	White uncoated tablets		
Identification code	Tablet	Tw174	
	Package		
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	8.5		
Thickness (mm)	4.5		
Weight (mg)	265		

INDICATIONS

Improvement of the following symptoms attributable to hypocalcemia:
Tetany, tetany-related symptoms
Calcium supplement in the following metabolic bone disorders:
Osteoporosis, osteomalacia
Calcium supplementation during the period of developmental growth, calcium supplementation during pregnancy/lactation

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 1.2 g of calcium aspartate daily in 2 or 3 divided doses. The dosage may be adjusted according to the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration

(Calcium L-Aspartate should be administered with care in the following patients.)

1) Patients receiving active vitamin D preparations [Hypercalcemia is likely to develop in such patients.]
2) Patients receiving digitalis preparations (See "Drug Interactions.")
3) Patients whose disease status is likely to lead to hypercalcemia

2. Important Precautions

Long-term Calcium L-Aspartate administration may lead to increased blood/urine calcium concentrations; thus, it is recommended that **periodic blood or urine calcium measurements be performed** during long-term therapy with this product.
If hypercalcemia develops, Calcium L-Aspartate administration should be discontinued.

3. Drug Interactions

Precautions for coadministration (Calcium L-Aspartate should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Digitalis preparations Digoxin Digitoxin	Coadministration of Calcium L-Aspartate with digitalis preparations may induce digitalis intoxication (arrhythmia, shock). Monitoring for absence/presence of digitalis intoxication and electrocardiography should be performed periodically, and blood digitalis concentrations should be measured as necessary. If any such abnormalities are noted, dosage reduction or discontinuation of digitalis preparations should be performed.	Coadministration of Calcium L-Aspartate with digitalis preparations may lead to increased effects of digitalis preparations
Tetracycline antibiotics Tetracyclines	Coadministration of Calcium L-Aspartate with tetracycline antibiotics may lead to decreased effects of such antibiotics. The concurrent use of Calcium L-Aspartate with tetracyclines should be avoided. If this product is to be used in combination with tetracyclines, precautions should be taken, including setting dosing intervals of ≥ 1 to 3 hours between this product and such antibiotics.	Calcium ions chelate tetracyclines, thereby inhibiting the absorption of tetracycline antibiotics.
New quinolone antibacterial agents	Coadministration of Calcium L-Aspartate with new quinolone antibacterial agents	Calcium ions chelate new quinolones, thereby inhibiting the

Ciprofloxacin hydrochloride Norfloxacin Tosufloxacin tosilate hydrate	may lead to decreased effects of such antibacterial agents. The concurrent use of Calcium L-Aspartate with new quinolones antibacterial agents should be avoided. If this product is to be used in combination with new quinolones antibacterial agents, precautions should be taken, including setting dosing intervals of ≥ 2 hours between this product and such antibacterial agents.	absorption of new quinolone antibacterial agents, and the resulting inhibition leads to decreased blood quinolone concentrations.

4. Adverse Reactions

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

If any of the following adverse reactions is observed, appropriate measures such as discontinuing administration should be taken.

	Incidence unknown
Long-term administration	Hypercalcemia, calculosis
Gastrointestinal	Abdominal distention, heartburn, soft stools
Others	Headache, epigastric discomfort, rash

5. Use in the Elderly

Since elderly patients often have reduced physiological functions, careful supervision and measures such as reducing the dose are recommended.

6. Pediatric Use

The use of Calcium L-Aspartate in low birth weight infants, neonates, and nursing infants is not recommended. [It has been reported that, in juvenile mice and rats (≤ 3 weeks after birth) given aspartate 250 mg/kg, histopathological changes were observed in the hypothalamic arcuate nucleus.]

7. Precautions Concerning Use

Precautions regarding dispensing:

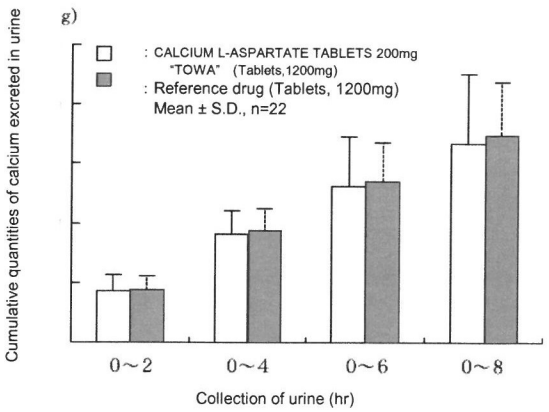
For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in severe complications such as mediastinitis.]

PHARMACOKINETICS

1. Bioequivalence test

In a cross-over study, single doses of 6 tablets of Calcium L-Aspartate Tablets 200mg "TOWA" and 6 tablets of a reference drug (equivalent to 1200 mg of calcium l-aspartate (anhydride)) were orally administered to healthy adult men (n = 22) under fasting conditions; the quantities of calcium excreted in urine were measured and data obtained on pharmacokinetic parameters (Ae, Umax) were statistically analyzed using the 90% confidence interval (CI). The analysis results showed that the 90% CI was within the range from log (0.80) to log (1.25), confirming the bioequivalence of these drugs.[1)]

(Note) Oral administration of 1200 mg in a single dose is beyond the approved dosage of Calcium L-Aspartate Tablets 200mg "TOWA."



	Ae_8 (mg)	Umax (mg/hr)
CALCIUM L-ASPARTATE TABLETS 200mg "TOWA" (Tablets, 1200mg)	16.73±7.02	2.53±1.03
Reference drug (Tablets, 1200mg)	17.41±5.69	2.60±0.84

(Mean ± S.D., n=22)

*Ae: Cumulative quantities of calcium excreted in urine

Umax: Maximum calcium excretion rate in urine

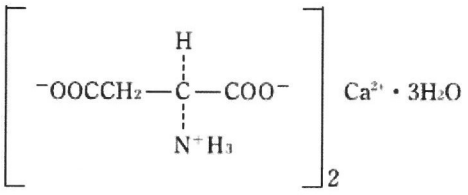
Quantities of calcium excreted in urine and parameters such as Ae and Umax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile

CALCIUM L-ASPARTATE TABLETS 200 mg "TOWA" have been confirmed to conform to the corresponding dissolution standards of Calcium L-Aspartate Tablets defined in the third section of the Japanese Pharmaceutical Codex[2)].

PHYSICOCHEMISTRY

Structural formula:



Nonproprietary name:
Calcium L-Aspartate Hydrate

Commonly used name:
Calcium L-Aspartate

Molecular formula:
$C_8H_{12}CaN_2O_8 \cdot 3H_2O$

Molecular weight:
358.31

Description:
Calcium L-Aspartate occurs as white crystalline powder. It is odorless or has a slightly bitter taste. It is freely soluble in water, and practically insoluble in ethanol (95), in diethyl ether and in chloroform. It is hygroscopic.

PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), CALCIUM

L-ASPARTATE TABLETS 200mg "TOWA" was estimated to be stable for 3 years under normal distribution conditions[3].

PACKAGING

CALCIUM L-ASPARTATE TABLETS 200 mg "TOWA" :
Boxes of 100 tablets, 1,000 tablets (PTP)
Polyethylene containers of 500 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
3) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

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