Revised: November 2016 (17th version, revision associated with revision of Japanese Pharmacopoeia)
Revised: June 2013 (16th version)

Japanese Pharmacopoeia
L-Carbocisteine Tablets

CARBOCISTEINE TABLETS 250mg "TOWA"
CARBOCISTEINE TABLETS 500mg "TOWA"

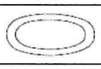
Storage:
Store at room temperature.
Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 872233		
	Tablets 250mg	Tablets 500mg
Approval No.	22500AMX00424	22500AMX00421
Date of listing in the NHI reimbursement price	June 2013	June 2013
Date of initial marketing in Japan	July 1990	July 2006
Date of reevaluation (quality)	February 2004	-
Date of addition of indication	September 1991	-

CONTRAINDICATIONS (Carbocistein Tablets is contraindicated in the following patients.)

Patients with a history of hypersensitivity to any of the ingredients of this product.

DESCRIPTION

		CARBOCISTEINE TABLETS 250mg "TOWA"	CARBOCISTEINE TABLETS 500mg "TOWA"
Active ingredient per tablet		L-Carbocisteine (JP) ····· 250mg	L-Carbocisteine (JP) ····· 500mg
Inactive ingredient		Corn Starch, Microcrystalline Cellulose, Hydroxypropylcellulose, Low Substituted Hydroxypropylcellulose, Magnesium Stearate, Light Anhydrous Silicic Acid, Talc, Titanium Oxide	Partially Hydrolyzed Polyvinyl Alcohol, Croscarmellose Sodium, Magnesium Aluminometasilicate, Magnesium Stearate, Hypromellose, Hydroxypropylcellulose, Talc, Titanium Oxide
Product description		White film-coated tablets	White film-coated tablets with a score
Identification code	Tablet	Tw710	Tw715
	Package		
Appearance	Top surface		
	Bottom surface		
	Side surface		
	Diameter (mm)	9.6	15.7/7.4 (major axis/minor axis)
	Thickness (mm)	4.7	5.1
	Weight (mg)	366	556

INDICATIONS

- Expectoration in the following disease
  Upper respiratory tract inflammation (pharyngitis, laryngitis), acute bronchitis, bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis
- Drainage in chronic sinusitis

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 500mg of L-Carbocisteine at a time 3 times daily.
The dosage may be adjusted according to the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration

(Carbocistein Tablets should be administered with care in the following patients.)

1) Patients with hepatic disorder [Following carbocisteine administration in patients with hepatic impairment, aggravated hepatic function may be observed.]
2) Patients with cardiac disorder [It has been reported that similar drugs of carbocisteine adversely affected patients with cardiac failure.]

2. Adverse Reactions

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

1) Clinically significant adverse reactions (incidence unknown)

(1) **Mucocutaneous ocular syndrome (Stevens-Johnson syndrome),toxic epidermal necrolysis (Lyell syndrome)**: Mucocutaneous ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored, and if such symptoms occur, administration of this product should be discontinued and appropriate measures should be taken.

(2) **Hepatic impairment, jaundice**: Hepatic impairment or jaundice associated with increased AST (GOT), ALT (GPT), or Al-P may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.

(3) **Shock, anaphylactoid reaction**: Shock or anaphylactoid reaction (dyspnea, edema, urticaria, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.

2) Other adverse reactions

	Incidence unknown
Gastrointestinal	Anorexia, diarrhea, abdominal pain, nausea, vomiting, abdominal distension, thirst, etc.
Hypersensitivity*)	Rash, eczema, erythema, edema, pyrexia, dyspnea, etc.
Others	Irritation

*): Administration of this product should be discontinued.

3. Use in the Elderly

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

4. Use during Pregnancy, Delivery or Lactation

It is not recommended to administer this product to pregnant women or women who may possibly be pregnant. [The safety of this product in pregnant women has not been established.]

5. 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

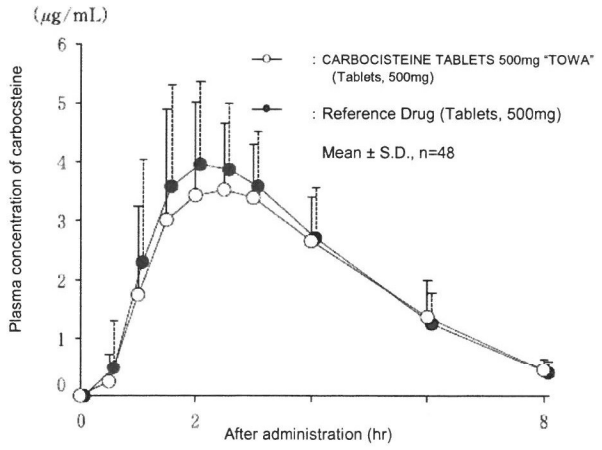
1. Bioequivalence test

1) CARBOCISTEINE TABLETS 250mg "TOWA"

The application for approval of Carbocisteine Tablets 250 mg "TOWA" was submitted based on "Handling of materials to be attached at the time of application for drug manufacturing/import approval" (PAB notification No. 718 dated May 30, 1980) and the manufacturing approval of this product was then obtained.

2) CARBOCISTEINE TABLETS 500mg "TOWA"

One tablet each of CARBOCISTEINE TABLETS 500mg "TOWA" and a reference drug (as 500 mg of L-Carbocisteine) were administered orally as a single dose to healthy adult men under fasting conditions (n=48) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs within the range between log (0.80) and log (1.25).



	Determined parameter		Reference parameter	
	AUC_8 (μg·hr/mL)	Cmax (μg/mL)	Tmax (hr)	$T_{1/2}$ (hr)
CARBOCISTEINE TABLETS 500 mg "TOWA" (Tablets, 500mg)	15.685±3.364	4.199±1.157	2.51±0.96	1.5613±0.2811
Reference drug (Tablets, 500mg)	16.751±3.164	4.725±1.158	2.27±0.87	1.4840±0.1861

(Mean ± S.D., n=48)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile

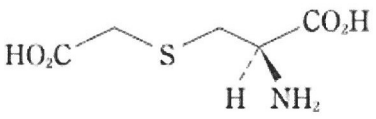
CARBOCISTEINE TABLETS 250mg "TOWA" and CARBOCISTEINE TABLETS 500mg "TOWA" have been confirmed to conform to the corresponding dissolution standards of L-Carbocisteine tablets defined in the third section of the Japanese Pharmaceutical Codex[2) 3)].

PHARMACOLOGY

Carbocisteine normalizes the composition ratio of sialic acid and fucose in sputum (regulation of contents in airway mucus) in patients with chronic airway disease and facilitates the repair of ciliated bronchiolar epithelial cells (normalization of airway mucosa) in patients with chronic bronchitis. In patients with chronic sinusitis, carbocisteine improves reduced nasal mucociliary clearance and repairs paranasal sinus mucosal disorder. Carbocisteine also facilitates the excretion of fluids accumulated in the middle ear cavity and normalizes the middle ear mucosa.[4)]

PHYSICOCHEMISTRY

Structural formula:



Nonproprietary name:
L-Carbocisteine
Chemical name:
(2*R*)-2-Amino-3-carboxymethylsulfanyl-propanoic acid
Molecular formula:
$C_5H_9NO_4S$
Molecular weight:
179.19
Description:
L-Carbocisteine occurs as a white crystalline powder. It is odorless, and has a slightly acid taste.
It is very slightly soluble in water, and practically insoluble in ethanol (95). It dissolves in dilute hydrochloric acid or in sodium hydroxide TS.
Melting point:
About 186°C (with decomposition)

PRECAUTIONS FOR HANDLING

Stability test

1) CARBOCISTEINE TABLETS 250mg "TOWA"
A long-term storage study using final packaging products (at 25°C and 60% relative humidity for 3 years) has proved that CARBOCISTEINE TABLETS

250mg "TOWA" is stable for 3 years under normal distribution conditions in the market[5].

2) CARBOCISTEINE TABLETS 500mg "TOWA"
In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), CARBOCISTEINE TABLETS 500mg "TOWA" were estimated to be stable for 3 years under normal distribution conditions[6]

PACKAGING

CARBOCISTEINE TABLETS 250mg "TOWA":
Boxes of 100 tablets, 1000 tablets,
Polyethylene containers of 1000 tablets
CARBOCISTEINE TABLETS 500mg "TOWA":
Boxes of 100 tablets, 1000 tablets,
Polyethylene containers of 500 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test (500mg)
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test (250mg)
3) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test (500mg)
4) The 15th revision Japanese Pharmacopoeia explanatory, C-995, 2006
5) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test (250mg)
6) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test (500mg)

Manufacturer and Distributor
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