Revised: ** February 2018 (12th version, Section of Adverse Reactions)
Revised: * December 2013 (11th version)

Oral Proteolytic Enzyme Inhibitor
Prescription-only drug*1)

CAMOSTAT MESILATE TABLETS 100mg "TOWA"

Standard Commodity Classification No. of Japan 873999	
Approval No.	22500AMX01134
Date of listing in the NHI reimbursement price	December 2013
Date of launch in Japan	July 1996
Date of reevaluation (quality)	October 1999
Date of addition of indication	March 2001

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

*1) Caution - Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (Camostat Mesilate Tablets is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any of the ingredients of this product

COMPOSITION AND PRODUCT DESCRIPTION

Active ingredient per tablet	Camostat Mesilate (JP)····· 100 mg		
Inactive ingredient	Lactose Hydrate, Hydroxypropylcellulose, Carmellose Calcium, Magnesium Stearate, Hypromellose, Macrogol 6000, Talc, Titanium Oxide		
Product description	White to pale yellowish white film-coated tablets		
Identification code	Tablet	Tw243	
	Package		
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	6.6		
Thickness (mm)	4.1		
Weight (mg)	130		

INDICATIONS
1. Remission of acute symptom in chronic pancreatitis
2. Postoperative reflux esophagitis

DOSAGE AND ADMINISTRATION
1. Remission of acute symptom in chronic pancreatitis
The usual dosage for oral use is 600mg of camostat mesilate daily in 3 divided doses. The dosage may be adjusted according to the patient's symptoms.
2. Postoperative reflux esophagitis
The usual dosage for oral use is 300mg of camostat mesilate daily in 3 divided doses after each meal.

PRECAUTIONS
1. **Careful Administration** (Camostat Mesilate tablets should be administered with care in the following patients.)
Patients with hypersensitivity [In case patients have hypersensitivity, adverse reactions may be induced.]

2. **Important Precautions**
1) This product should not be administered in patients with severe chronic pancreatitis requiring suction of gastric juice, or dietary restrictions such as fasting and abstention from drinking.
2) This product should not be used for the treatment of postoperative reflux esophagitis due to reflux of gastric juice since the efficacy of this product cannot be expected.
3) If improvement of symptoms of postoperative reflux esophagitis is not observed, then the therapy with this product should not be continued aimlessly for a long-term period.

3. **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) **Shock, anaphylaxis:** Shock, anaphylaxis may occur. Patients should be carefully monitored, and if any abnormalities such as decreased blood pressure, dyspnea, and pruritus are observed, administration of this product should be discontinued and appropriate measures should be taken.
(2) **Thrombocytopenia:** Thrombocytopenia may occur. If such symptoms occur, the dosage should be reduced or administration of this product should be discontinued.
(3) **Hepatic function disorder, and jaundice:** Hepatic function disorder, jaundice associated with marked increased AST (GOT), ALT (GPT), γ-GTP or Al-P may occur. Patients should be carefully closely monitored, if any abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.
(4) **Hyperkalemia:** Serious hyperkalemia may occur. Patients should be closely monitored by examinations including serum electrolyte tests. If any such abnormalities are observed, administration of this product should be discontinued, and appropriate treatment should be given.

2) Other adverse reactions

	Incidence unknown
Hematologic	Leucopenia, erythrocytopenia, eosinophilia
Hypersensitivity note2)	Rash, pruritus, etc.
Gastrointestinal	Nausea, abdominal discomfort, abdominal distention, diarrhea, anorexia, vomiting, thirst, heartburn, abdominal pain, constipation
Hepatic	Increased AST (GOT), increased ALT (GPT)
Renal	Increased BUN, increased creatinine
Others	Edema, hypoglycemia

Note 2) If any symptom occurs, administration of this product should be discontinued.

4. Use during Pregnancy, Delivery or Lactation

Large doses of this product should not be used in pregnant women or in women who may possibly be pregnant. [Animal experiments (in rats) have reported that administration of this drug at doses not less than 40 times the human therapeutic dose (400 mg/kg/day) resulted in suppression of fetal weight gain.]

5. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants and children has not been established. (No clinical experience)

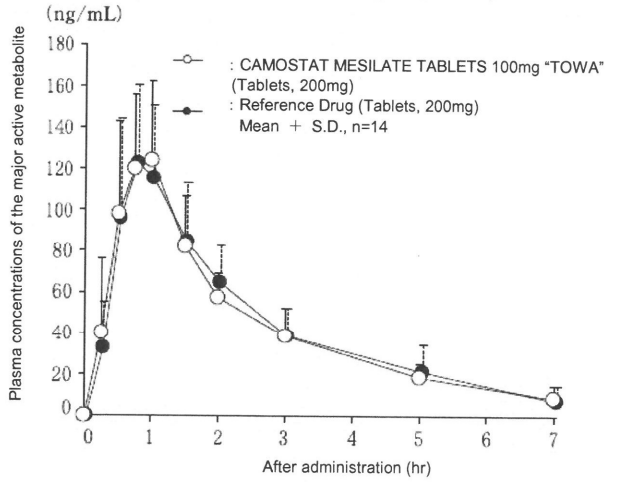
6. Precautions Concerning Use

Precautions Concerning the Dispensing of the Drug:
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 2 tablets of Camostat Mesilate Tablets 100mg "TOWA" and 2 tablets of a reference drug (equivalent to 200 mg of camostat mesilate) were orally administered to healthy adult men (n = 14) under fasting conditions; plasma concentrations of the major active metabolite of 4-(4-guanidinobenzoyloxy) phenylacetate were measured and data obtained on pharmacokinetic parameters (AUC, Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs (based on PAB Notification No. 718 dated May 30, 1980) [1].



	Determined parameter		Reference parameter	
	AUC_7 (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
CAMOSTAT MESILATE TABLETS 100mg "TOWA" (Tablets, 200mg)	300.0±67.0	142.3±35.0	0.84±0.19	1.98±0.82
Reference drug (Tablets, 200mg)	305.1±82.4	138.5±34.3	0.82±0.18	1.82±0.59

(Mean ± S.D., n=14)

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

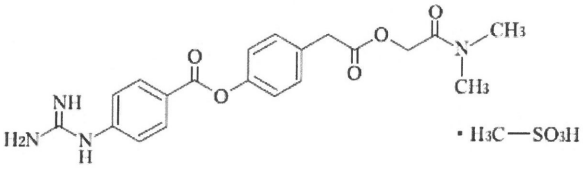
Camostat Mesilate Tablets 100mg "TOWA" has been confirmed to conform to the corresponding dissolution standards of Camostat Mesilate tablets defined in the third section of the Japanese Pharmaceutical Codex [2].

PHARMACOLOGY

This product, which is a protease inhibitor, has the effect to inhibit trypsin, plasma kallikrein, plasmin, kallidinogenase, thrombin, C_{1r}, and C_1-esterase. This product has weak effects on pancreatin and pancreatic kallikrein, and has no effects on α-chymotrypsin, pepsin, bromelain, semi-alkaline proteinase or serrapeptase. The circulating metabolite of 4-(4-guanidinobenzoyloxy) phenylacetic acid converted from orally administered this product shows activity comparable with that of this product. When administered to animals with experimentally induced pancreatitis, this product has a life-prolonging effect. This product also has the effects to relax the Oddi's sphincter and inhibit blood coagulation and the fibrinolytic system [3].

PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name:
Camostat Mesilate
Chemical name:
Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy) phenylacetate monomethanesulfonate
Molecular formula:
$C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$
Molecular weight:
494.52
Description:
Camostat Mesilate occurs as white, crystals or crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (95), and practically insoluble in diethyl ether.
Melting point:
194-198°C

PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), CAMOSTAT MESILATE TABLETS 100mg "TOWA" was estimated to be stable for 3 years under normal distribution conditions [4].

PACKAGING

CAMOSTAT MESILATE TABLETS 100mg "TOWA":
Boxes of 100 tablets, 1,000 tablets (PTP)
Polyethylene containers of 1,000 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test

2) Internal data of Towa Pharmaceutical Co., Ltd.:
Dissolution test
3) The 16th revision Japanese Pharmacopoeia
explanatory, C-1106, 2011
4) Internal data of Towa Pharmaceutical Co., Ltd.:
Stability test

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