

Revised: August 2009 (11<sup>th</sup> version of new form)

Standard Commodity Classification No. of Japan
873999

- Oral protease inhibitor -  
**FOIPAN<sup>®</sup> Tablets 100mg**

&lt; Camostat mesilate tablets &gt;

Prescription drug

<b>Storage</b>
Store at room temperature.

<b>Expiration date</b>
The expiration date is indicated on the package (3 years).

Approval No.	21700AMZ00621
Date of listing in the NHI reimbursement price	December 2005
Date of initial marketing in Japan	January 2006
Date of latest reexamination	January 2003 (Foipan Tablets)
Date of latest approval of indications	July 1994 (Foipan Tablets)

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

**CONTRAINDICATIONS (FOIPAN<sup>®</sup> is contraindicated in the following patients.)**

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

**DOSAGE AND ADMINISTRATION****1. Remission of acute symptoms of chronic pancreatitis**

The usual dosage for oral use is 600 mg of camostat mesilate daily in three divided doses. The dosage may be adjusted according to the patient's symptoms.




**2. Postoperative reflux esophagitis**

The usual dosage for oral use is 300 mg of camostat mesilate daily in three divided doses after each meal.

**DESCRIPTION****1. Composition**

<b>Brand name</b>	FOIPAN <sup>®</sup> Tablets 100 mg
<b>Ingredient/content (Content per tablet)</b>	Camostat mesilate 100 mg
<b>Inactive ingredient</b>	Hydroxypropylcellulose, Carmellose calcium, Magnesium stearate, Polyoxyethylene (105) polyoxypropylene (5) glycol, Lactose hydrate
<b>Dosage form</b>	Film-coated tablets

**2. Product description**

<b>Appearance</b>	<b>Face</b>	
	<b>Back</b>	
	<b>Edge</b>	
<b>Diameter (mm)</b>	6.6	
<b>Thickness (mm)</b>	4.0	
<b>Weight (mg)</b>	About 126	
<b>Color</b>	White to yellowish white	
<b>Identification code</b>	ONO 305	

**INDICATIONS**

1. Remission of acute symptoms of chronic pancreatitis
2. Postoperative reflux esophagitis

**PRECAUTIONS****1. Careful Administration (FOIPAN<sup>®</sup> should be administered with care in the following patients)**

Patient with hypersensitivity [In case patients have hypersensitivity, adverse reactions may be induced.]

**2. Important Precautions**

- (1) FOIPAN<sup>®</sup> should not be administered in patients with severe chronic pancreatitis requiring suction of gastric juice, or dietary restrictions such as fasting and abstinence 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****<Remission of acute symptoms of chronic pancreatitis>**

Eighty three adverse reactions to FOIPAN<sup>®</sup>, including abnormal laboratory test values, were observed in 69 (1.8%) of 3,806 patients evaluated in the investigation conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were rash in 15 inci-

dences (0.4%), pruritus in 9 incidences (0.2%), nausea in 10 incidences (0.3%), abdominal discomfort in 7 incidences (0.2%), abdominal fullness in 6 incidences (0.2%), etc. (At the end of the reexamination period)

#### <Postoperative reflux esophagitis>

Seventy five adverse reactions to FOIPAN<sup>®</sup>, including abnormal laboratory test values, were observed in 57 (1.3%) of 4,224 patients evaluated in the investigation conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were hepatic function abnormalities such as increased AST (GOT) · ALT (GPT) in 12 incidences (0.3%), diarrhea in 8 incidences (0.2%), nausea in 5 incidences (0.1%), etc. (At the end of the reexamination period)

### (1) Clinically significant adverse reactions

#### 1) Shock or anaphylactoid symptoms

Shock or anaphylactoid symptoms (both incidences unknown\*) may occur. Patients should be carefully monitored. If any symptoms such as decreased blood pressure, dyspnea and pruritus are observed, administration should be discontinued and appropriate measures be taken.

#### 2) Thrombocytopenia

Thrombocytopenia (incidence unknown\*) may occur rarely. If such symptoms are observed, the dose should be reduced or administration should be discontinued.

#### 3) Hepatic function disorder or jaundice

Hepatic function disorder accompanied by remarkable increase of AST(GOT), ALT(GPT),  $\gamma$ -GTP, Al-P, or jaundice (both incidences unknown\*) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate therapeutic measures such as discontinuing the administration should be taken.

#### 4) Hyperkalaemia

Severe hyperkalaemia (incidence unknown\*) may occur. Patients should be carefully monitored by conducting serum electrolyte tests. If any abnormalities are observed, administration should be discontinued and appropriate measures be taken.

### (2) Other adverse reactions

	0.5%>	≥0.1%	<0.1%	Incidence unknown*
Hematologic			Leukopenia, erythrocytopenia	Eosinophilia
Hypersensitivity <sup>Note)</sup>	Rash, pruritus, etc.			
Gastrointestinal	Nausea, abdominal discomfort, abdominal fullness, diarrhea		Anorexia, vomiting, dry mouth, heartburn, abdominal pain, constipation	
Hepatic	Increased AST (GOT)·ALT(GPT), etc.			
Renal			Increased BUN, increased creatinine	
Others			Edema, hypoglycemia	

\* The ADRs classified into “Incidence unknown” is the ones collected from spontaneous reports.

Note)

If such symptoms are observed, administration 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 shown 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.<sup>1)</sup>

### 5. Pediatric Use

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

### 6. Precautions concerning Use

Precautions regarding dispensing :

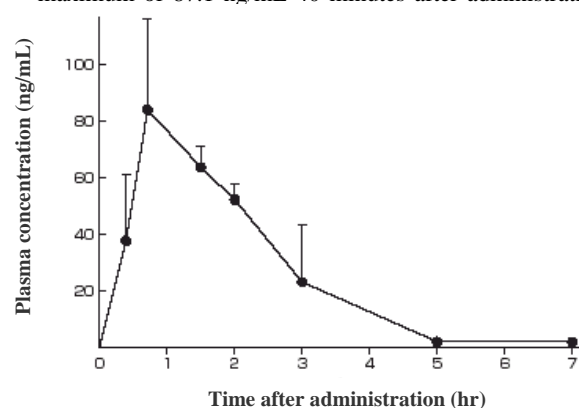
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. (It has been reported that if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa resulting in severe complications such as mediastinitis.)

## PHARMACOKINETICS

### 1. Blood concentration

#### (1) Healthy adults

When a single dose of camostat mesilate at 200 mg was orally administered to 5 healthy adults in the fasted state, the plasma concentration of its active metabolite, 4-(4-guanidinobenzoyloxy) phenylacetate, reached a maximum of 87.1 ng/mL 40 minutes after administration,



Plasma concentration of the active metabolite, 4-(4-guanidinobenzoyloxy) phenylacetate

T <sub>max</sub> (min)	C <sub>max</sub> (ng/mL)	AUC (ngb min/mL)	T <sub>1/2</sub> (min)
40	87.1 ± 29.5	10,400 ± 1,400	100 ± 40

Data except T<sub>max</sub> are shown as mean ± SD.

T<sub>max</sub> is shown as median

## (2) Patients with gastrectomy

When a single dose of camostat mesilate at 100 mg was orally administered to 4 patients with total gastrectomy or subtotal gastrectomy in the fasted state, the maximum plasma concentration was 30 ng/mL, changing at a similar level to healthy volunteers.<sup>3)</sup>

## 2. Metabolism

Carboxylate ester moiety of camostat mesilate is hydrolyzed to an active metabolite 4-(4-guanidinobenzoyloxy) phenylacetate, which is further hydrolyzed to 4-guanidinobenzoic acid.<sup>4)</sup>

Camostat mesilate is mainly hydrolyzed by carboxylesterase and 4-(4-guanidinobenzoyloxy) phenylacetate by arylesterase (*in vitro*).<sup>5)</sup>

Camostat mesilate and its metabolite 4-(4-guanidinobenzoyloxy) phenylacetate did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (*in vitro*).<sup>6)</sup>

## 3. Excretion

When a single dose of camostat mesilate at 200 mg was orally administered to 5 healthy adults in the fasted state, urinary metabolites were accounted for mostly by 4-guanidinobenzoic acid and for only a small proportion, by 4-(4-guanidinobenzoyloxy) phenylacetate. The rates of urinary excretion at 5 - 6 hours after administration were 20% and 0.8%, respectively, and little was further recovered in urine during later periods.<sup>2)</sup>

## 4. Protein binding rate

The protein-binding rate to human serum was 25.8 – 28.2% (*in vitro*).

## CLINICAL STUDIES

### 1. Remission of acute symptoms of chronic pancreatitis

(1) The usefulness of FOIPAN<sup>®</sup> in the improvement rates of principal symptoms of chronic pancreatitis such as pain, tenderness, urine amylase level, nausea-vomiting, flatulence was recognized with a significant difference compared with that in the control group in patients with chronic pancreatitis in a double-blind comparative clinical study.<sup>7)</sup>

(2) FOIPAN<sup>®</sup> showed symptomatic improvement in pain, tenderness, serum and urine amylase level, etc. with an efficacy rate of 48.6% (155/319 patients with chronic pancreatitis) in the clinical studies including the double-blind comparative clinical study.<sup>8)</sup>

### 2. Postoperative reflux esophagitis

FOIPAN<sup>®</sup> showed symptomatic improvement in erosion, hemorrhage, etc. endoscopically as well as in subjective symptoms such as heartburn, chest pain, hot feeling in the chest etc., with an efficacy rate of 82.0% (132/161 patients with postoperative reflux esophagitis) in the clinical studies including the double blind comparative clinical study.<sup>9)</sup>

## PHARMACOLOGY

### 1. Pharmacological effects

#### (1) Inhibitory effect on proteolytic enzymes

- 1) Camostat mesilate exhibits a potent inhibitory effect on trypsin, plasma kallikrein, plasmin, thrombin, C<sub>1r</sub> and C<sub>1</sub> esterase (*in vitro*).<sup>10)</sup> On the other hand, it shows a weak inhibitory effect on pancreatin and pancreatic kallikrein and has no inhibitory effect on  $\alpha$ -chymotrypsin, pepsin, bromelain, semialkaline protease and serratiopeptidase (*in vitro*).<sup>11)</sup> An active metabolite in blood, 4-(4-guanidinobenzoyloxy) phenylacetate, after oral administration of camostat mesilate, is nearly equipotent with the mother compound in these inhibitory activities (*in vitro*).<sup>12)</sup>
- 2) Oral administration of camostat mesilate in rats at doses of 50 - 500 mg/kg caused a dose-dependent, rapid elevation of anti-trypsin and anti-plasmin activities in blood.<sup>13)</sup> A dose-dependent increase of anti-kallikrein activity in blood was also observed after oral administration of 200 and 600 mg to healthy adult volunteers.<sup>2)</sup>

#### (2) Inhibitory effect on the kinin formation system

In a perfusion experiment with rat hind limbs immersed in warm water at 46°C, oral administration of camostat mesilate at 25 and 100 mg/kg inhibited the release of kinin-like substances by 32 - 41% and 70 - 80%, respectively.<sup>14)</sup>

#### (3) Inhibitory effect on the coagulation and fibrinolytic systems

In rabbits with increased fibrinolysis, camostat mesilate administered orally at doses of 50 - 200 mg/kg inhibited clot lysis, an elevation of FDP and prolongation of thrombin time in a dose-dependent manner and thereby reducing hemorrhage.<sup>15)</sup>

#### (4) Effects on experimental pancreatitis

- 1) In rats with experimental pancreatitis induced by retrograde infusion of bile acids and trypsin into the pancreatic duct, oral administration of camostat mesilate at 25 - 100 mg/kg decreased mortality in a dose-dependent manner.<sup>16)</sup>
- 2) Intraduodenal administration of camostat mesilate in rats (5 mg/kg) and dogs (10 mg/kg) with experimental pancreatitis induced by duodenal loop obstruction suppressed manifestation of pancreatic edema and an elevation of protease activities in blood, thereby decreasing mortality.<sup>17)</sup>
- 3) In mice with ethionine-induced experimental pancreatitis after feeding choline deficient diet, oral administration of camostat mesilate at 20 - 300 mg/kg b.i.d. inhibited the elevation of protease activities in the pancreas, thereby decreasing mortality.<sup>18)</sup>

#### (5) Effect on experimental postoperative reflux esophagitis

- 1) Oral administration of camostat mesilate at 100 mg/kg b.i.d. from postoperative Day 2 for 5 days in rats with experimental postoperative reflux esophagitis suppressed ulceration of esophageal mucosa.<sup>19)</sup>

- 2) Oral administration of camostat mesilate at 50 mg t.i.d. from postoperative Day 14 for 14 days in dogs with experimental postoperative reflux esophagitis improved endoscopic findings of esophageal erosion and hemorrhage, and showed therapeutic efficacy.<sup>20)</sup>
- 3) Oral administration of camostat mesilate at 100 mg/kg in rats with experimental postoperative reflux esophagitis suppressed trypsin activity in collected digestive fluid by 81.8%.<sup>19)</sup>

## 2. Mechanism of action

It has been recognized that camostat mesilate, after oral administration, acts promptly on kinin formation, fibrinolytic, coagulation and complementary systems to immediately inhibit enzyme activities and their abnormal increases. It thereby proves to be effective in remission of inflammatory symptoms and pain as well as in improvement of serum amylase level in chronic pancreatitis. It also proves to be effective in improvement of postoperative reflux esophagitis by inhibiting trypsin in regurgitated peptic juice in the esophagus.

## PHYSICOCHEMISTRY

Nonproprietary name:

Camostat mesilate

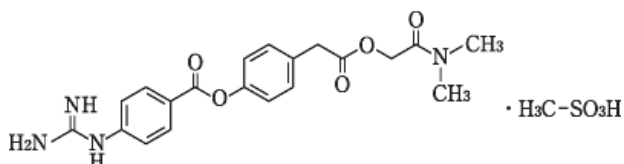
Chemical name:

Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy) phenylacetate monomethanesulfonate

Molecular formula:  $C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$

Molecular weight: 494.52

Structural formula:



Description:

Camostat mesilate occurs as white crystals or a 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

Dispensing FOIPAN<sup>®</sup> with olmesartan medoxomil as a "one-dose pack" should be avoided. (In case of storing the one-dose pack containing FOIPAN<sup>®</sup> and olmesartan medoxomil under conditions of high temperature and high humidity, the discoloration of FOIPAN<sup>®</sup> tablets may occur.)

## PACKAGING

### FOIPAN<sup>®</sup> Tablets 100 mg:

Boxes of 100, 200, 420, 500, 1,000 and 1,050 tablets in press-through packages and bottles of 500 and 1,000 tablets

## REFERENCES

- 1) Ichikawa Y. et al.: Gendai Iryo, **12** (Extra issue): 127, 1980.
- 2) Hiraku S. et al.: Iyakuhin Kenkyu, **13**: 756, 1982.
- 3) Yamamoto T. et al.: Changes in plasma concentration of camostat mesilate in patients with gastrectomy. Internal data of Ono Pharmaceutical Co., Ltd.
- 4) Ohki S. et al.: Gendai Iryo, **12** (Extra issue): 71, 1980.
- 5) Nemoto H. et al.: The enzymes involved in the metabolism of camostat mesilate. Internal data of Ono Pharmaceutical Co., Ltd.
- 6) Matsunaga N. et al.: The effect of camostat mesilate on CYP 450 isozymes. Internal data of Ono Pharmaceutical Co., Ltd.
- 7) Ishii K. et al.: Gendai Iryo, **16**: 844, 1984 and 1 other report.
- 8) Pooled analyses of clinical data on <Chronic pancreatitis>. Internal data of Ono Pharmaceutical Co., Ltd.
- 9) Pooled analyses of clinical data on < Postoperative reflux esophagitis >. Internal data of Ono Pharmaceutical Co., Ltd.
- 10) Tamura Y. et al.: Biochim. Biophys. Acta., **484**: 417, 1977.
- 11) Kayama N. et al.: Gendai Iryo, **12** (Extra issue): 1, 1980.
- 12) Kayama N. et al.: Inhibitory concentration of active metabolites of camostat mesilate. Internal data of Ono Pharmaceutical Co., Ltd.
- 13) Kayama N. et al.: Gendai Iryo, **12** (Extra issue): 11, 1980.
- 14) Obata T. et al.: Gendai Iryo, **12** (Extra issue): 19, 1980.
- 15) Obata T. et al.: Gendai Iryo, **12** (Extra issue): 27, 1980.
- 16) Okegawa T. et al.: Gendai Iryo, **12** (Extra issue): 5, 1980.
- 17) Takasugi S. et al.: Digestion, **24**: 36, 1982.
- 18) Okegawa T. et al.: Gendai Iryo, **12** (Extra issue): 41, 1980.
- 19) Kawabata K. et al.: Japanese Pharmacology and Therapeutics, **20**: 3517, 1992.
- 20) Watanabe M. et al.: Gendai Iryo, **26** (Extra issue): 2983, 1994.

## REQUEST FOR LITERATURE SHOULD BE MADE TO:

Copies of the company's internal reports that are cited in the list of references above can also be requested at the following address:

Ono Pharmaceutical Co., Ltd.  
Pharmacovigilance Division  
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Tel: 0120-626-190

## Manufactured and marketed by:

Ono Pharmaceutical Co., Ltd.  
8-2, Kyutaromachi 1-chome, Chuo-ku, Osaka, 541-8564

## BRAND NAMES IN OTHER COUNTRIES

FOIPAN<sup>®</sup> (R.O.K.)