Revised: May 2013(10th version)

Standard Commodity Classification No. of Japan
87449, 87219

Phosphodiesterase inhibitor
-Agent for Ameliorating Cerebro-Vascular Disorders and Bronchial Asthma-

KETAS® Capsules 10 mg

< Ibudilast >

Storage
Store at room temperature (1~30°C) See "PRECAUTIONS FOR HANDLING".

Expiration date
This product should be used before the expiration date specified on the package.

Approval No.	20100AMZ00027000
Date of listing in the NHI reimbursement price	April 1989
Date of initial marketing in Japan	May 1989
Date of latest reexamination	March 1996
Date of latest reevaluation	December 2001
International birth date	May 1989

CONTRAINDICATIONS (KETAS® Capsules 10mg is contraindicated in the following patients.)
Patients whose intracranial hemorrhages are supposed not to have been stopped [Completion of hemostasis may be delayed.]

Identification code	ケタス10mg (on capsule)	
	KP-305 (on package)	
Others	This product is a sustained release preparation containing white sustained release granules and enteric sustained release granules.	

DESCRIPTION

Product description

Brand Name	KETAS® Capsules 10 mg	
Active ingredient	Ibudilast 10 mg: The Japanese Pharmacopoeia (JP)	
Inactive ingredient	Contents within capsule	Lactose Hydrate, microcrystalline cellulose, povidone, aminoalkyl - methacrylate- copolymer RS, polyoxy-methylene hydrogenated castor oil 60, macrogol 6000, sodium chloride, hydruos silicon dioxide, methacrylate-copolymer L, magnesium stearate
	Capsule itself	Titanium oxide, sodium lauryl sulfate, gelatin
Type of capsule	#3 hard capsule	
Color	Cap	White
	Body	White
Appearance	Front side / Back side	

INDICATIONS

1. Bronchial asthma
2. Improvement of dizziness secondary to chronic cerebral circulation impairment associated with sequelae of cerebral infarction.

DOSAGE AND ADMINISTRATION

1. In case of bronchial asthma
   The usual adult dosage for oral use is 10 mg of ibudilast twice daily.
2. In case of cerebro-vascular disorders
   The usual dosage for oral use is 10 mg of ibudilast three times daily. The dosage may be adjusted according to the patient's symptoms.

<Precautions>

In case of sequelae of cerebral infarction
Administration periods should be decided carefully with the consideration of clinical efficacy and adverse reactions. If any expected effect is not observed after 12-week administration, the drug should be discontinued.

PRECAUTIONS

1. Careful Administration (This product should be administered with care in the following patients.)

1) Patients under acute phase of cerebral infarction
[The symptom may be exacerbated.]
2) Patients with impaired hepatic function
3) Elderly patients
[See PRECAUTIONS 4."Use in the Elderly" section]

2. Important Precautions

1) In case of bronchial asthma
Since this product does not ameliorate immediately the attack already evoked, patients should be informed well the nature of this product.
2) The patients with bronchial asthma under long-term treatment with steroids
Reducing the dose of steroids with this product should be made gradually under enough control.

3. Adverse Reactions

<At the end of the re-examination period>
Adverse reactions to this drug, including abnormal laboratory tests, were observed in 507 (3.39%) of 14,968 patients treated. The most freqently observed adverse reactions were anorexia in 87 patients (0.58%), nausea in 84 patients (0.56%), increased AST(GOT) levels in 45 patients (0.30%), increased ALT(GPT) levels in 53 patients (0.35%) and increased r-GTP levels in 54 patients (0.36%).

1) Clinically significant adverse reaction

(1) Thrombocytopenia
Thrombocytopenia may occur. Patients must therefore be carefully monitored. If any of abnormal findings are observed, administration should be discontinued and appropriate therapeutic measures must be taken.

(2) Hepatic dysfunction, Jaundice
Hepatic dysfunction or jaundice with increased AST (GOT), ALT (GPT), Al-P, γ -GTP and/or total bilirubin may occur. Patients should be carefully monitored. If any symptoms are observed, administration should be discontinued and appropriate therapeutic measures must be taken.

2) Other adverse reactions

	5% > ≥0.1%	**<0.1%**
Hypersensitivity symptoms*	Rash	Itching, etc.
Psychoneurologic	Dizziness, headache	Tremor, insomnia, sleepiness, apathy, etc.
Gastrointestinal	Anorexia, nausea, vomiting, abdominal pain, dyspepsia	Feeling of Enlarged abdomen, diarrhea, gastric ulcer, etc.
Cardiovascular		Palpitation, orthostatic hypotension, hot flushes
Hematologic		Anemia, leukopenia
Hepatic	Elevation of AST(GOT), ALT(GPT), ALP, γ -GTP	Elevation of total bilirubin
Others		Malaise, tinnitus, facial edema, floating feeling, taste abnormality, etc.

Note
If any of these symptoms are observed, the drug should be discontinued.

4. Use in the Elderly

This product is metabolized mainly by the liver. Because there is a possibility of persistently elevated blood concentrations in elderly patients, who often have liver hypofunction, this product should be administered carefully with special attention to the dosage.

5. Use during Pregnancy, Delivery or Lactation

1) This product is not recommended to use in pregnant women or in women who may possibly be pregnant.
[Retardation in the growth of newborn in laboratory animals (rats) caused by this product was reported. [1)2)]]
2) Use of this drug in lactating women is not recommended.
[It was reported that this product was excreted into breast milk in animal studies (rats).[3)]]

6. Pediatric Use

The safety of this product in children has not been established. (There is insufficient clinical data in pediatric patients.)

7. Precautions concerning Use

1) Precaution during oral administration

Since this product is made as a sustained release preparation, the contents of capsule should not be taken out from capsule and dispensed.

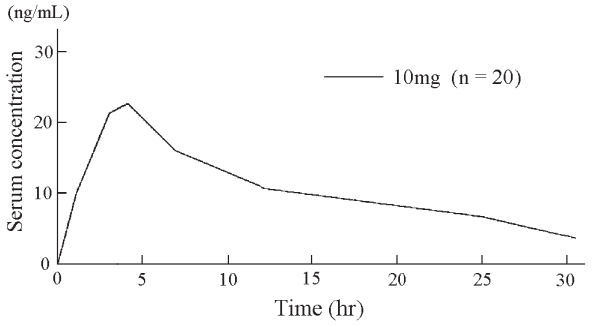
2) Precautions regarding dispensing

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 concentrations [4)]

Blood concentrations and pharmacokinetic parameters of ibudilast after a single oral dose of 10mg to the healthy adults are shown below.



Pharmacokinetic parameters

Dose (mg)	Tmax (hr)	Cmax (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0\rightarrow30}$ (ng▪hr/mL)
10	4	25	12.0	334

2) Metabolism and Excretion [5)]

Following a single dose of 10mg ibudilast to healthy adults, about 60% of the dose was excreted as metabolites in urine by 72 hours. Unchanged form was not detected in urine, and main metabolites were 6,7-dihydrodiol form, 2beta, 3beta-diol form and their conjugations.

CLINICAL STUDIES

1. Bronchial asthma (dose, 20 mg/d)

The clinical efficacy of this product in clinical studies including double blind clinical studies is summarized as follows.

Double blind clinical study has demonstrated that this product is effective to treat bronchial asthma.

Type of disease	Improvement rate (%)	
	Moderate to marked	Slight to marked
Atopy	44.3 (74/167)	78.4 (131/167)
Mixed	39.6 (101/255)	71.4 (182/255)
Infective	40.7 (24/ 59)	67.8 (40/ 59)
Total	41.4 (199/481)	73.4 (353/481)

2. Cerebrovascular disorders (dose, 30mg/d) [6)]

The clinical usefulness of this product on improvement of dizziness for the patients with sequelae of cerebral infarction is shown as follows. This clinical usefulness was demonstrated from a double blind clinical study.

In this study, this product or placebo was administrated for 8 weeks after the preceding observation period for 4 weeks. In the observation period, placebo was administrated and the patients with poor compliance or without firm symptoms were eliminated from the study followed-on.

Drug	Improvement of dizziness	
	Improvement rate (%)	Wilcoxon's test
Ibudilast	50.0 (47/ 94)	P<0.001
Placebo	18.7 (20/ 107)	

PHARMACOLOGY

1. For cerebrovascular disorders.

1) Clinical pharmacological actions

(1) Increasing action on cerebral blood flow

Ibudilast increased cerebral blood flow in patients with cerebro-vascular disorders. (PET). [7)]

(2) Blood flow improvement in the internal carotid artery

Ibudilast increased patient's blood flow in average and diminish the resistance to blood flow in circulation system.[8)]

(3) Inhibition of platelet activation

Ibudilast inhibited platelet activation in patients with erebro-vascular disorders.[9)]

(4) Inhibition of platelet coagulation

Ibudilast inhibited platelet coagulation in patients with cerebro-vascular disorders.[9)10)]

(5) Protective effects

Ibudilast inhibited adhesion molecule expression on vascular endothelid cell in patients with cerebral infarction. [11)]

2) Basic pharmacological actions

Phosphodiesterase Inhibition

Ibudilast inhibited the activity of Phosphodiesterase from human heart and brain which were obtained by RT-PCR cloning.[12)]

(1) Vasodilatory actions

Ibudilast potentiated vasorelaxation mediated by prostacyclin in isolated canine basilar artery.[13)]

And Ibudilast increased cerebral blood flow in rat cerebral infarction models.That increase rate was higher than that of normal rats. [14)]

(2)Anti-inflammatory effects

Ibudilast suppressed TNFα and NO production by glial cell.[15)] And, Ibudilast protected cerebrovascular white matter from lesions at optic tract ,internal capsule,callosum under in chronic cerebral hypoperfus model in rats.[16)]

(3)Anti-thrombogenetic actions

Ibudilast inhibited thrombogenicity in gerbil model of carotid artery thrombosis[17)],and the flattening of EEG wave after peripheral vascular occlusion in rat thromboembolism model. [18)]

(4) Neuroprotective actions

Ibudilast inhibited damage induced by glutamatic acid on the hippocampal nerve in rat model.[19)]

And Ibudilast ameliorated the reduction of the nerve cell density induced by ischemia in rat model of transient cerebral ischemia.[20)]

2. For bronchial asthma

1) Clinical pharmacological action

(1) Amelioration of airway hypersensitivity

Ibudilast was shown to ameliorate the airway hypersensitivity in asthmatic patients in provocation test with methacholine. [21)]

(2) Suppression of bronchial responses induced by antigen inhalation

Ibudilast was observed to prevent the both immediate [22)] and delayed asthmatic responses [23)] in bronchial asthmatic patients in provocation test with inhalated antigen.

2) Basic pharmacological action

(1) Inhibition of phosphodiesterase from eosinophil and bronchial smooth muscle

Ibudilast inhibited the hosphodiesterase from guinea pig eosinophil and bovine bronchial smooth muscle. [24)]

(2) Attenuation of airway hyperresponsiveness

Ibudilast attenuated the airway hyper-responsiveness induced by PAF in guinea pigs.[25)]

(3) Leukotriene/PAF antigonism

Ibudilast selectively inhibited leukotriene D_4 or PAF induced constriction in guinea pig tracheal muscle preparations, [26) 27)] and in airway of anesthetized guinea pigs[28) 29)] or cats [30)]. Also, ibudilast inhibited the increment of vascular permeability induced by leukotriene D_4 or PAF in guinea pigs [29)].

(4) Inhibition of leukotriene release

Ibudilast inhibited leukotriene C_4/B_4 release from peripheral leukocytes from healthy volunteers or asthmatic patients. [31)]

(5) Inhibition of experimental asthma

Ibudilast inhibited airway constriction in guinea pig and rat experimental asthmatic models. [32)] Inhibitory action of ibudilast was also significant in the experimental models strongly mediated by endogenous leukotriene. [28)]

(6) Promotion of secretion and mucociliary transport activity in airway tract

Ibudilast was suggested to enhance secretion of respiratory tract fluid with lower viscosity in rats. [33)] Also, ibudilast increased mucociliary transport activity in frog palatine mucosa. [34)]

PHYSICOCHEMISTRY

Nonproprietary name:

Ibudilast (JAN)

Chemical name:

1-[2-(1-Methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-methylpropan-1-one

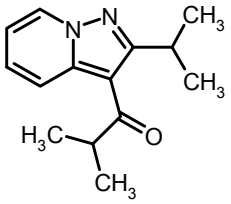
Molecular formula:

$C_{14}H_{18}N_2O$

Molecular weight:

230.31

Structural formula:



Description:

White crystalline powder.

Very soluble in methanol, freely soluble in ethanol (99.5) or acetic anhydride and very slightly soluble in water.

Melting point:

54-58°C

Partition coefficient:

Organic phase	Aqueous phase	Partition coefficient
1-Octanol	Water	2.57×10^3
Chloroform	Water	2.40×10^4

(at 25ºC)

PRECAUTIONS FOR HANDLING

1. This product is designated drug.
2. Expiration date: This product should be used before the expiration date specified on the package.
3. Storage: This product should be stored at room temperature (1-30°C).

PACKAGING

KETAS Capsules 10 mg:

PTP pack: Boxes of

100 capsules (10 capsules × 10)
500 capsules (10 capsules × 50)
1000 capsules (10 capsules × 100)
2100 capsules (21 capsules×100)
in press-through packages.

Bottles of 500 capsules.

REFERENCES

1) Imai S., et al., The Clinical Report, 20, 101 (1986)
2) Imai S., et al., Administration study of Ibudilast during peri- and post-natal period and lactation period in rat (In-house data)
3) Takagi K., et al., Oyo Yakuri, 30, 967 (1985)
4) Maeda S., et al., The Clinical Report, 23, 2349 (1989)
5) Uchida H., et al., The Clinical Report, 19, 6220 (1985)
6) Shinohara Y., et al., Neurological Therapeutics., 19(2), 177 (2002)
7) Fukuyama H., et al., Neurol. Res., 15, 169 (1993)
8) Morimoto M., et al., Geriat. Med., 30(9), 1497 (1992)
9) Murashima M., et al., J. New Remedies & Clinics., 40(1), 28 (1991)
10) Uchiyama S., et al., J. New Remedies & Clinics, 42(9), 1868 (1993)
11) Nomura K., et al., Jpn. J. Stroke, 27, 304 (2005)
12) Gibson LCD., et al., Eur. J. Pharmacol., 538(24), 39 (2006)
13) Ohashi M., et al., Arch. Int. Pharmacodyn.Ther., 280(2), 216 (1986)

14) Kudo Y., et al., Folia Pharmacol. Japon., 85, 435 (1985)
15) Suzumura A., et al., Brain Research, 837, 203 (1999)
16)Wakita H., et al., Brain Research, 992, 53 (2003)
17) Nishimura H., et al., Stroke, 27 , 1099 (1996)
18) Ohashi M., et al., Gen. Pharmacol., 17, 385 (1986)
19) Tominaga Y., et al., Clin. Exp. Pharmacol. Physiol., 23, 519 (1996)
20)Yoshioka M., et al., Pharmacol. Res., 45(4), 305 (2002)
21) Sakakibara H., et al., Jpn. Pharmacol. Ther., 13, 7469 (1985)
22) Kounou O., et al., Jpn. Pharmacol. Ther., 13, 7477 (1985)
23) Adachi M., et al., Jpn. Pharmacol. Ther., 14, 1013 (1986)
24) John E. S., et al., Br. J. Pharmacol., 111, 1081 (1994)
25) Eda K., et al., Japan J. Pharmacol., 46(suppl.), 282 (1988)
26) Nagai H., et al., Japan J. Pharmacol., 33, 1215 (1983)
27) Ohashi M., et al., Prostaglandins, 32, 875 (1986)
28) Ohashi M., et al., Am. Rev. Respir. Dis., 133, A213 (1986)
29) Eda K., et al., Japan J. Pharmacol., 43(suppl.), 178 (1987)
30) Ichinose M., et al., Resp. Res., 5, 110 (1986)
31) Tamura G., et al., The Clinical Report, 20, 181 (1986)
32) Nishino K., et al., Folia Pharmacol. Japon., 83, 281 (1984)
33) Ohashi M., et al., The Clinical Report, 19, 5471 (1985)
34) Noda Y., et al., Jpn. J. Allergol., 38, 434 (1989)

REQUEST FOR LITERATURE SHOULD BE MADE TO:

A request for in-house data mentioned in the References can also be made to the following.

Kyorin Pharmaceutical Co., Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
Tel. 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday excluding national holidays)

Manufactured and marketed by:

Kyorin Pharmaceutical Co., Ltd.
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