

Revised: July 2009 (8th version)

Standard Commodity Classification No. of Japan
873959

- Thrombolytic agents -

Cleactor[®] for i.v. Inj 400,000**Cleactor[®]** for i.v. Inj 800,000**Cleactor[®]** for i.v. Inj 1,600,000

<Monteplase (genetical recombination) preparation>

Biological products and Prescription drug

	For i.v. Injection 400,000	For i.v. Injection 800,000	For i.v. Injection 1,600,000
Approval No.	22000AMX01389000	22000AMX01385000	22000AMX01386000
Date of listing in the NHI reimbursement price	Jun 2008	Jun 2008	Jun 2008
Date of initial marketing in Japan	Jun 1998	Jun 1998	Jun 1998
Date of latest approval of indication	Jul 2005		
Date of latest reexamination	Mar 2009		
International birth date	Apr 1998		

Storage
CLEACTOR should be stored at room temperature.

Expiration date
CLEACTOR should be used before the expiration date indicated on the package or label.

Caution : CLEACTOR should be used promptly after reconstitution.

Caution - Use only as directed by a physician.

WARNING

CLEACTOR has been reported to cause cerebral hemorrhage with an occasionally fatal outcome. (See "Adverse Reactions" section.)

Patients should be carefully screened on the basis of the "Contraindications" and "Precautions" sections before using CLEACTOR. When using CLEACTOR for patients with acute pulmonary embolism, the dosage should be carefully determined on the basis of the "Contraindications" and "Precautions" sections. During and after treatment with the drug, patients should be closely monitored for the possible occurrence of bleeding complications by such measures as frequent blood examination (including blood coagulation test, etc.) and clinical observation.

CONTRAINDICATIONS (CLEACTOR is contraindicated in the following patients.)

- (1) Patients with concurrent hemorrhage such as gastrointestinal hemorrhage, urinary tract hemorrhage, retroperitoneal hemorrhage, intracranial hemorrhage or hemoptysis [CLEACTOR may promote hemorrhage and prevent hemostasis.]
- (2) Patients who have had an intracranial or spinal operation or injury (within last 2 months)
- (3) Patients with an intracranial tumor, arteriovenous malformation or aneurysm
- (4) Patients with bleeding disposition
- (5) Patients with serious hypertension
[Rationale for the contraindications (2) - (5): CLEACTOR may induce hemorrhage and prevent hemostasis.]

DESCRIPTION

CLEACTOR is a white, freeze-dried injection which should be dissolved prior to use. Each vial of CLEACTOR contains the following components. When CLEACTOR is dissolved in the following volumes of isotonic sodium chloride solution, JP, the resultant solution shows the following pH and osmotic pressure ratio values.

		CLEACTOR for i.v. Injection 400,000	CLEACTOR for i.v. Injection 800,000	CLEACTOR for i.v. Injection 1,600,000
Active ingredient	Monteplase (genetical recombination)	400,000IU	800,000IU	1,600,000IU
Inactive ingredients	L-Aspartic acid	17.6mg	35.2mg	70.4mg
	L-Arginine	19.2mg	38.4mg	76.8mg
	Hydrochloric Acid	q.s.		
	Sodium Hydroxide	q.s.		
	D-Mannitol	76.8mg	153.6mg	307.2mg
Volume of isotonic sodium chloride solution, JP (80,000IU/mL)		5mL (per vial)	10mL (per vial)	20mL (per vial)
pH		4.8-5.4		
Osmotic pressure ratio		1.4-1.5		

(IU:International Units)

In the production process of CLEACTOR, the following materials are used.

Recombinant baby hamster kidney cells, Fetal bovine serum, Plasmin prepared from bovine serum, Trypsin prepared from porcine pancreas, Anti-monteplase monoclonal antibodies prepared from mouse ascites and Anti-impure proteins antibodies prepared from rabbit serum

INDICATIONS

- Lysis of coronary thrombus caused by acute myocardial infarction (within 6 hours of the onset of symptoms)
- Lysis of pulmonary artery thrombus caused by acute pulmonary embolism with hemodynamic instability

<Precautions>

1. It is recommended that acute pulmonary embolism should be diagnosed after thrombosis, other emboli or obstruction of blood flow have been confirmed by pulmonary angiography or other diagnostic tests. However, if either of these tests is not available, CLEACTOR may be administered to patients who are highly suspected clinically to have acute pulmonary embolism with hemodynamic instability and have been confirmed by tests to have such symptoms as hypoxemia or acute right heart strain.
2. It is recommended that CLEACTOR should be administered to patients with acute pulmonary embolism in combination with background therapy of anticoagulant medication including heparin.

DOSAGE AND ADMINISTRATION

- Lysis of coronary thrombus caused by acute myocardial infarction (within 6 hours after the onset of symptoms):
The usual adult dosage for intravenous injection is 27,500 IU/kg body weight of alteplase (genetical recombination).
- Lysis of pulmonary artery thrombus caused by acute pulmonary embolism with hemodynamic instability:
The usual adult dosage for intravenous injection is 13,750 up to 27,500 IU/kg body weight of alteplase (genetical recombination). Maximal dosage is 27,500 IU/kg at one time.
During reconstitution, it should be dissolved in isotonic sodium chloride solution, JP at a concentration of 80,000 IU/mL. The prepared solution should be infused at a rate of about 10 mL (800,000 IU) /min. Administration of CLEACTOR should be initiated as soon as possible after the onset of symptoms.

<Precautions>

When using CLEACTOR for patients with acute pulmonary embolism, it is recommended that the dosage should be decided carefully with consideration given to the possible risks and benefits of treatment, because hemorrhagic adverse events occur dose-dependently. When using CLEACTOR for patients with acute pulmonary embolism having a high risk of bleeding, such as those described in the "Careful Administration" section, it is recommended that adoption of a low dosage (13,750 IU/kg) be considered.

PRECAUTIONS

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

- (1) Elderly patients (aged 65 years or over) (see paragraph (3) - 1) and (5) - 3) of "Important Precautions" section.)
- (2) Patients who have recently undergone major surgery, organ biopsy or vascular puncture (e.g., intra-arterial injection or arterial puncture) (within last 10 days)

- (3) Patients who have suffered a recent trauma (within last 10 days)
- (4) Patients with a history of cerebrovascular disorders
- (5) Patients with a peptic ulcer, digestive tract diverticulitis or colitis
- (6) Patients with active tuberculosis
- (7) Menstruating patients or those who have delivered recently or gone into labour prematurely or had an abortion within last 10 days
- (8) Patients with hemorrhagic diabetic retinopathy or other hemorrhagic ophthalmologic disease
[Rationale for conditions (2) - (8) : CLEACTOR may induce hemorrhage.]
- (9) Patients with suspected left atrial thrombosis (e.g., patients with mitral stenosis accompanying atrial fibrillation)
[Such patients may induce cerebral embolism.]
- (10) Patients with subacute bacterial endocarditis or acute pericarditis
[Such patients may induce cerebral embolism or pericardial effusion.]
- (11) Patients with cerebral infarction
[Such patients may induce hemorrhagic cerebral infarction.]
- (12) Patients with serious hepatic or renal function disorders
[Reduced metabolism/excretion may result in enhancement of the effect of CLEACTOR.]
- (13) Patients currently being treated with anticoagulants, antiplatelet agents or any other thrombolytic agents (see "Drug Interactions" section.)
- (14) Patients with a history of hypersensitivity to CLEACTOR or any other peptide/protein preparations

2. Important Precautions

- (1) CLEACTOR should be administered intravenously as a bolus injection and not as an infusion.
- (2) CLEACTOR should be administered in a CCU or equivalent facility so that the patient's condition can be closely monitored by ECG or arterial blood gases, etc. Appropriate measures should be taken if any adverse reactions occur during or after treatment with the drug.
- (3) Compared with conventional t-PA preparations, CLEACTOR has a higher potential for inducing bleeding complications. More specifically, **CLEACTOR may cause serious bleeding complications such as cerebral hemorrhage**, so careful attention should be paid to the following points:
 - 1) **In patients treated at doses higher than the usual recommended dose and elderly patients of 75 years or over** there may be an increased risk of cerebral hemorrhage. In such patients, the risk/benefit ratio of CLEACTOR should be strictly assessed in comparison with other therapeutic approaches available.
[In clinical trials with CLEACTOR conducted on patients with acute myocardial infarction, cerebral hemorrhage occurred in elderly patients aged over 65 years and when it was used at doses higher than that recommended, the risk of cerebral hemorrhage in-

creased. In the case of conventional t-PA preparations, the risk of cerebral hemorrhage has been reported to increase in patients of 75 years and over.]

- 2) CLEACTOR may cause bleeding complications.
When any other thrombolytic agent is coadministered with CLEACTOR, adequate precautions should be taken (e.g., the thrombolytic agent should be commenced at least 60 min after the administration of CLEACTOR and restricted to the minimum dose required) because the earlier or unrestricted administration of other thrombolytic agents may increase the duration or severity of bleeding. When an anticoagulant or an antiplatelet agent is to be administered relatively soon after CLEACTOR, the patient should be closely monitored for possible bleeding complications by such measures as frequent blood examination (including blood coagulation test, etc) and clinical observation, because the use of anticoagulants or antiplatelet agents soon afterwards increases the risk of bleeding complications. Prior to the administration of any such drugs, their therapeutic necessity should be strictly assessed and the both timing of administration and dosage carefully determined. (See paragraphs (5) - 5) and (6) - 1) of “Important Precautions” section, and “Drug Interactions” section.)
- 3) During and after the administration of CLEACTOR, patients should be carefully observed to ensure early detection of the symptoms/signs of bleeding complications. For this purpose, blood examination (including blood coagulation test, etc.) should also be performed frequently.
- 4) To prevent bleeding from the injection site, appropriate methods of arteriovenous puncture or post-injection management should be devised. Especially, the site of arterial puncture should be carefully observed.
- (4) The readministration of CLEACTOR should be performed with caution because some patients may show an **allergic reaction (such as anaphylaxis)** to this peptide preparation upon re-exposure. If anaphylactoid reaction occurs, treatment should be immediately discontinued and appropriate measures taken.
- (5) When using CLEACTOR for patients with acute myocardial infarction, attention must be paid to the following points.
 - 1) It is recommended that the administration of CLEACTOR should be initiated after thrombosis has been confirmed by coronary angiography. However, if coronary angiography is not possible, CLEACTOR may be administered to patients who have severe chest pain, are unresponsive to coronary vasodilators and have obvious ST elevation on an ECG.
 - 2) Since coronary recanalization following thrombolysis may induce **arrhythmia (reperfusion-associated arrhythmia)**, the patient should be closely monitored by ECG for the possible occurrence of **serious arrhythmias such as ventricular fibrillation or ventricular tachycardia**. If any such arrhythmia occurs, appropriate measures should be taken immediately.
- 3) Full attention should be given to the risk of cardiac rupture, ventricular septal perforation, and pericardial effusion leading to cardiac tamponade after starting the administration of CLEACTOR. Since elderly patients (aged 65 years or over) are especially at risk of developing cardiac rupture and ventricular septal perforation, the risk/benefit ratio of CLEACTOR in such patients should be carefully considered in comparison with other therapeutic approaches available. [In clinical trials with CLEACTOR conducted on patients with acute myocardial infarction elderly patients (age 65 years or over) or patients with anterior myocardial infarction were found to be significant risk factors for the development of cardiac rupture, ventricular septal perforation and pericardial effusion during or after treatment with CLEACTOR.]
- 4) Administration of CLEACTOR should be initiated within 6 hr of the onset of symptoms of myocardial infarction.
- 5) Heparin may be administered at the same time as or after CLEACTOR to prevent the recurrence of occlusion. However, since the coadministration with heparin may cause **serious bleeding complications such as cerebral hemorrhage**, heparin therapy should be postponed until **6 hr after the administration of CLEACTOR** whenever possible. [In clinical trials with CLEACTOR conducted on patients with acute myocardial infarction, cerebral hemorrhage occurred when heparin was given by intravenous infusion between 4 and 6 hr after administration of CLEACTOR.]
- (6) When using CLEACTOR for patients with acute pulmonary embolism, attention must be paid to the following points.
 - 1) When the coadministration of heparin is used as background therapy, bleeding must be checked for and the dosage of heparin adjusted if necessary because of the risk of bleeding with such therapy. (See paragraph (5)-5) of “Important Precautions”)
 - 2) After the administration CLEACTOR, full attention must be given to the possibility of embolism relapse.

3. Drug Interactions

Precautions for coadministration (CLEACTOR should be administered with care when coadministered with the following drugs or when they are to be given soon after using CLEACTOR.)

Although CLEACTOR is usually administered as a bolus intravenous injection over 2 - 3 min, its effect is sustained for a long period. Therefore, when any other thrombolytic agent is coadministered with CLEACTOR, adequate precautions should be taken (e.g. therapy with such an agent should be initiated at least 60 min after the administration of CLEACTOR and it should be restricted to the minimum dose required). When another thrombolytic agent, an anticoagulant or antiplatelet agent is to be coadministered with CLEACTOR, the therapeutic necessity should be strictly assessed and the both timing of administration and dosage

should be carefully determined. In the case of coadministration of heparin, refer to (5)-5) and (6)-1) of “Important Precautions”.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Thrombolytic agents Tissue plasminogen activator [t-PA], Urokinase, Nasaruplase, etc.	An increase in bleeding tendency may produce serious hemorrhage.	The additive pharmacological effects of both drugs may increase the bleeding tendency.
Anticoagulants Heparin, Low-molecular-weight heparin, Warfarin potassium, Argatroban hydrate, Xa inhibitors, Dried concentrated human active protein C, etc.	An increase in bleeding tendency may produce serious hemorrhage.	Addition of the anticoagulant effect to the fibrinolytic effect of CLEACTOR may increase the bleeding tendency.
Antiplatelet agents Aspirin, Clopidogrel sulfate, Dipyridamole, Ticlopidine hydrochloride, etc.	An increase in bleeding tendency may produce serious hemorrhage.	Addition of the antiplatelet effect to the fibrinolytic effect of CLEACTOR may increase the bleeding tendency.

4. Adverse Reactions

Adverse reactions were reported in 307 of 3,283 patients (9.35%). In 3,218 patients with acute myocardial infarction, 376 patients (11.68%) experienced reperfusion-associated arrhythmias requiring specific measures (At latest re-examination of acute myocardial infarction indication).

Also, abnormal changes in laboratory test values were reported in 107 of 492 patients (21.75%, at latest approval of acute pulmonary embolism indication).

(1) Clinically significant adverse reactions

1) Serious hemorrhagic events:

Serious hemorrhagic events such as cerebral hemorrhage (5%> ≥0.1%), gastrointestinal hemorrhage (5%> ≥0.1%) or pulmonary hemorrhage (incidence unknown) may occur. Patients should be carefully observed and in the event of such symptoms, treatment with CLEACTOR should be discontinued and appropriate measures taken.

Owing to the possibility of a transfusion being required and that of hemorrhagic shock, caution should be exercised with respect to increase in hemorrhage.

2) Cardiac rupture, ventricular septal perforation and cardiac tamponade:

Cardiac rupture (5%> ≥0.1%), ventricular septal perforation (5%> ≥0.1%) and pericardial effusion leading to cardiac tamponade (0.1%>) may occur. Patients should be carefully observed and in the event of such symptoms, treatment with CLEACTOR should be discontinued and appropriate measures taken.

3) Ventricular fibrillation and ventricular tachycardia:

Serious arrhythmias such as ventricular fibrillation (5%> ≥0.1%) or ventricular tachycardia (5%> ≥0.1%) may occur in association with reperfusion. Patients should be closely monitored and appropriate measures immediately taken, if any such event occurs. (See Note 2) in “Other adverse reactions” section.)

4) Shock:

Since CLEACTOR may induce shock, patients should be carefully observed and if any symptoms such as decrease in blood pressure, diaphoresis, abnormal heart beat or dyspnea occur, treatment should be discontinued and appropriate measures taken.

(2) Other adverse reactions

	≥5%	5%> ≥0.1%	0.1%>
Hematologic <small>note 1)</small>	Erythrocytopenia, decrease in hemoglobin and hematocrit	Bleeding at the injection site, gingival bleeding, hematuria, oral hemorrhage, bleeding from wounds, subcutaneous hemorrhage and thrombocytopenia	
Cardiovascular	Arrhythmias <small>note 2)</small>	Pericardial effusion	Decrease in blood pressure
Respiratory			Dyspnea
Hypersensitivity <small>note 3)</small>			Rash
Hepatic		Elevation of ALT (GPT), AL-P, AST (GOT), LDH and total bilirubin	
Renal		Elevation of BUN, creatinine and urinary protein	
Gastrointestinal		Nausea and vomiting	
Others			Chill

Note

- 1) In the event of such symptoms, patients should be carefully observed during and after treatment with CLEACTOR.
- 2) The incidence (%) of various forms of reperfusion-associated arrhythmias requiring specific measures is shown below.

No. of patients	3,218
No. of patients with reperfusion-associated arrhythmias	376 (11.68)
Total number of arrhythmic events	425
Ventricular extrasystole	147 (4.57)
Ventricular tachycardia	121 (3.76)
Ventricular fibrillation	50 (1.55)
Sinus bradycardia	27 (0.84)
Idioventricular rhythm	16 (0.50)
Bradycardia	11 (0.34)
Complete atrioventricular block	10 (0.31)
Atrioventricular block	8 (0.25)
Ventricular arrhythmia	6 (0.19)
Sinus arrest	5 (0.16)
Accelerated idioventricular rhythm	4 (0.12)
Arrhythmia	3 (0.09)
Atrial fibrillation	3 (0.09)
Sinoatrial block	3 (0.09)
Supraventricular extrasystole	3 (0.09)
Supraventricular tachycardia	2 (0.06)
Ventricular bigeminy	2 (0.06)
Supraventricular arrhythmia	1 (0.03)
Second-degree atrioventricular block	1 (0.03)
Cardiac arrest	1 (0.03)
Extrasystole	1 (0.03)

Note

- 3) In the event of such symptoms, treatment should be discontinued and appropriate measures taken.

5. Use in the Elderly

Since elderly patients are especially at risk of bleeding CLEACTOR should be carefully administered. (See paragraph (3) - 1) of “Important Precautions” section.)

Also, elderly patients with myocardial infarction are especially at risk of developing cardiac rupture and ventricular

septal perforation, CLEACTOR should be carefully administered. (See paragraph (5)-3) of “Important Precaution” section.)

6. Use during Pregnancy, Delivery or Lactation

CLEACTOR should only be used in pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risks of with treatment.

[In an animal study (in rabbits) it has been reported that CLEACTOR has a tendency to increase the incidence of embryonal or fetal death, and abortion at high dosage. The fibrinolytic effect of CLEACTOR may cause placental detachment.]

7. Pediatric Use

The safety in children has not been established (no clinical experience).

8. Precautions concerning Use

Preparation

- (1) Use promptly after reconstitution.
- (2) CLEACTOR should only be reconstituted with isotonic sodium chloride solution, JP and should not be combined with other solutions.

<Reference>

Dosage according to body weight

Body Weight (kg)	Intravenous administration of 13,750IU/kg			Intravenous administration of 27,500IU/kg		
	Dosage (x10,000 IU)	Injection Volume (mL)	Injection Time (Sec)	Dosage (x10,000 IU)	Injection Volume (mL)	Injection Time (Sec)
30	41.25	5.2	30~45	82.50	10.3	60~90
35	48.13	6.0		96.25	12.0	
40	55.00	6.9		110.00	13.8	
45	61.88	7.7		123.75	15.5	
50	68.75	8.6	45~60	137.50	17.2	90~120
55	75.63	9.5		151.25	18.9	
60	82.50	10.3		165.00	20.6	
65	89.38	11.2		178.75	22.3	
70	96.25	12.0	60~75	192.50	24.1	120~150
75	103.13	12.9		206.25	25.8	
80	110.00	13.8		220.00	27.5	
85	116.88	14.6		233.75	29.2	
90	123.75	15.5	75~90	247.50	30.9	150~180
95	130.63	16.3		261.25	32.7	
100	137.50	17.2		275.00	34.4	

(IU: International Unit)

PHARMACOKINETICS

1. Blood Concentration

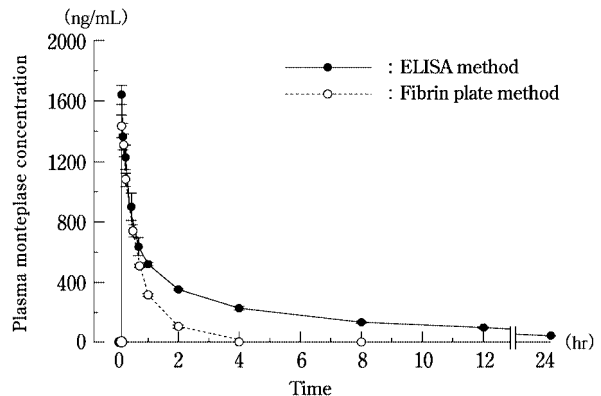
Monteplase (genetical recombination) was administered intravenously to healthy adult male volunteers at a single dose of 738,000 IU (6.0mg) for 3 min. The plasma monteplase concentration was determined by the ELISA or fibrin plate method. Plasma concentrations are shown in the graph below.

By the ELISA method, the mean plasma concentration was 1,643.45 ng/mL at 5 min after administration, and elimination thereafter followed a nearly biphasic pattern as determined. The elimination half-life was 23.66 min at the α -phase and 7.82 hr at the β -phase.

By the fibrin plate method, the mean plasma concentration was 1,492.63 ng/mL at 5 min after administration, and elimination thereafter followed a nearly biphasic pattern.

However, the concentration at the β -phase could not be determined except for the first one or two points due to low sensitivity. So the elimination half-life on the basis of analysis by the 1 compartment model was 29.43 min.

Within the dosage range from 61,500 to 738,000 IU, the peak plasma concentration and area under the plasma concentration-time curve increased dose-dependently. It was thus pharmacokinetically linear. ¹⁾



Plasma concentration after single intravenous administration of 738,000IU (6.0mg) of monteplase (Mean±S.E.M., n=4)

Pharmacokinetic parameters for single intravenous administration of 738,000 IU (6.0mg) of monteplase (upper column: ELISA method, lower column:fibrin plate method)

C_{max} (ng/mL)	AUC (ng · hr/mL)	$t_{1/2\alpha}$ (min)		$t_{1/2\beta}$ (hr)		CL (mL/min/Kg)
		$t_{1/2}$ (min)	$t_{1/2}$ (min)	$t_{1/2}$ (hr)	$t_{1/2}$ (hr)	
1,643.45	4,454.94	23.66	7.82	0.35		
±113.69	±587.05	±5.21	±0.57	±0.07		
1,492.63	1,081.53 (note)	29.43	1.41			
±165.75	±111.38	±4.58	±0.17			

(Mean±S.D., n=4)

Note) The values at 0 to 8 hrs were calculated by the trapezoidal method. CL was calculated on basis of the above values.

2. Urinary excretion

Monteplase (genetical recombination) was administered intravenously to healthy adult male volunteers at a single dose of 492,000 IU (4.0mg) for 3 min. When the urinary monteplase concentration was determined by the ELISA method, no monteplase could be detected. ¹⁾

CLINICAL STUDIES

Clinically efficacy

1. In a dose-finding study and double blind clinical trial conducted on patients with acute myocardial infarction, CLEACTOR was administered intravenously at a single dose of 27,500 IU/kg for about 2 min. The results are shown in the table below. ^{2, 3)}

The subjects of this study were administered CLEACTOR within 6 hr of the onset of acute myocardial infarction. Although they had been given nitrates by intracoronary administration before this, the injured coronary arteries were still observed to be completely occluded.

Clinical Trial	Recanalization Rate (TIMI grade: more than 2)		Global Improvement Rating (moderately to remarkably improved)
	30 min	60 min	
Dose-finding Study	52.9 % (27/51)	78.4 % (40/51)	78.4 % (40/51)
Double blind clinical trial	61.9 % (60/97)	79.4 % (77/97)	79.2 % (76/96)

2. In a dose-finding study and double blind clinical trial conducted on patients with acute pulmonary embolism, CLEACTOR was administered intravenously at a single dose of 13,750 IU/kg or 27,500 IU/kg for about 2 min. The results are shown in the table below.^{4, 5)}

The subjects of this study were administered CLEACTOR within 5 day of the onset of acute pulmonary embolism.

In all of them filling defects or obstruction of blood flow had been detected in pulmonary angiography

Clinical Trial		Improvement Rating for pulmonary thromboembolism blood flow ^{note)}	
		60 min	24~48 hr
Dose - finding Study	13,750 IU/kg	50.0% (7/14)	80.0% (12/15)
	27,500 IU/kg	93.3% (14/15)	100.0% (15/15)
Double blind clinical trial	27,500 IU/kg	84.6% (11/13)	

Note) Above results are based on pulmonary arteriography. Improvement ratings (moderately to remarkably improved) for pulmonary thromboembolism were based on blood flow improvement in segmental branches or above, or on shrinkage of pulmonary thromboembolism observable by the naked eye.

PHARMACOLOGY

1. Mechanism of Action

Monteplase has binding affinity with fibrin, and its plasminogen activating action is enhanced by fibrin. Monteplase thus binds with thrombosis and lyses it by decomposing the fibrin through activating plasminogen to plasmin.⁶⁾

2. Thrombolytic Action

In a canine model with coronary artery thrombi, a bolus injection of monteplase lyses thrombi dose-dependently, thereby recanalizing occluded coronary arteries. In this case the changes in the fibrinogen and plasminogen, the blood coagulating and fibrinolytic factor, was mild.⁷⁾

In a pig model of injured coronary artery endothelium, monteplase also recanalized occluded coronary arteries.⁸⁾

In a canine model with coronary artery thrombi, monteplase enabled left ventricular function to recover rapidly by recanalizing occluded coronary arteries.⁹⁾

In a mouse model of pulmonary embolism, monteplase was effective in suppressing fatality.¹⁰⁾

PHYSICOCHEMISTRY

Nonproprietary name:

Monteplase (genetical recombination) (JAN)

Monteplase (INN)

Entity:

Glycoprotein (molecular weight: ca.68,000; two-chain form 80% or over; 527 amino acid residues: ca.80%) consisting of 527 amino acid residues (C₂₅₆₉H₃₈₉₆N₇₄₆O₇₈₃S₃₉:

molecular weight: 59,009.49) and 530 amino acid residues (C₂₅₈₀H₃₉₁₆N₇₅₂O₇₈₆S₃₉: molecular weight: 59,293.80) produced in baby hamster kidney cells by expression of a modified human tissue plasminogen activator-cDNA, in which the nucleotide sequence coding for cysteine 84 is mutated to that for serine, derived from human Bowes melanoma-mRNA

Description:

Monteplase occurs as a colorless, clear solution.

It is odorless. (CLEACTOR crude solution)

CONDITIONS FOR APPROVAL

Post-marketing surveillance trials to assure safety and efficacy were to be conducted on patients with acute pulmonary embolism who were treated with CLEACTOR during the reexamination period as far as possible. The accumulated trial results were to be reported at regular intervals.

PACKAGING

CLEACTOR for i.v. Injection 400,000: 1 vial

CLEACTOR for i.v. Injection 800,000: 1 vial

CLEACTOR for i.v. Injection 1,600,000: 1 vial

REFERENCES

- 1) Onishi A. et al.: Jpn. J. Clin. Pharmacol., **25**, 551, 1994.
- 2) Kawai T. et al.: Jpn. Pharmacol. Ther., **22**, 3925, 1994.
- 3) Kawai T. et al.: *ibid.*, **22**, 4411, 1994.
- 4) Sugimoto T. et al.: Jpn. Pharmacol. Ther., **33**, 629, 2005.
- 5) Sugimoto T. et al.: Jpn. Pharmacol. Ther., **33**, 653, 2005.
- 6) Suzuki G et al.: *ibid.*, **22**, S-353, 1994.
- 7) Suzuki G et al.: *ibid.*, **24**, 1287, 1996.
- 8) Adachi H. et al.: Jpn. J. Pharmacol., **58**, 309, 1992.
- 9) Suzuki S. et al.: Jpn. Circ. J., **59**, 205, 1995.
- 10) Suzuki G. et al.: The Japanese Journal of Thrombosis and Hemostasis, **10**, 420, 2005.

REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

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Eisai Co., Ltd.

6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo 112-8088