KINLYTIC- urokinase injection, powder, lyophilized, for solution
ImaRx Therapeutics, Inc.

Kinlytic™
(urokinase for injection)

DESCRIPTION

Kinlytic™ (urokinase for injection) is a thrombolytic agent obtained from human neonatal kidney cells grown in tissue culture. The principal active ingredient of Kinlytic™ is the low molecular weight form of urokinase, and consists of an A chain of 2,000 daltons linked by a sulfhydryl bond to a B chain of 30,400 daltons. Kinlytic™ is supplied as a sterile lyophilized white powder containing 250,000 international units urokinase per vial, mannitol (25 mg/vial), Albumin (Human) (250 mg/vial), and sodium chloride (50 mg/vial).

Following reconstitution with 5 mL of Sterile Water for Injection, USP, Kinlytic™ is a clear, slightly straw-colored solution; each mL contains 50,000 international units of urokinase activity, 0.5% mannitol, 5% Albumin (Human), and 1% sodium chloride (pH range 6.0 to 7.5).

Thin translucent filaments may occasionally occur in reconstituted Kinlytic™ vials (see **DOSAGE AND ADMINISTRATION**).

Kinlytic™ is for intravenous infusion only.

Kinlytic™ is produced from human neonatal kidney cells (see **WARNINGS**). No fetal tissue is used in the production of Kinlytic™. Kidney donations are obtained exclusively in the United States from neonates (birth to 28 days) for whom death has not been attributed to infectious causes and that have exhibited no evidence of an infectious disease based in part, on an examination of the maternal and neonatal donor medical records. The maternal and neonatal donor screening process also identifies specific risk factors for known infectious diseases and includes testing of sera for HBV, HCV, HIV-1, HIV-2, HTLV-I, HTLV-II, CMV, and EBV. Donors with sera testing positive or associated with other risk factors are excluded. During the manufacturing process, cells are tested at multiple stages for the presence of viruses using *in vitro* and *in vivo* tests that are capable of detecting a wide range of viruses. Cells are also screened for HPV using a DNA detection-based test and for reovirus using a polymerase chain reaction-based test. The manufacturing process used for this product has been validated in laboratory studies to inactivate and/or remove a diverse panel of spiked model enveloped and non-enveloped viruses, and includes purification steps and a heat treatment step (10 hours at 60°C in 2% sodium chloride). A single vial of Kinlytic™ contains urokinase produced using cells derived from one or two donors.

CLINICAL PHARMACOLOGY

Urokinase is an enzyme (protein) produced by the kidney, and found in the urine. There are two forms of urokinase which differ in molecular weight but have similar clinical effects. Kinlytic™ is the low molecular weight form. Kinlytic™ acts on the endogenous fibrinolytic system. It converts plasminogen to the enzyme plasmin. Plasmin degrades fibrin clots as well as fibrinogen and some other plasma proteins.

Information about the pharmacokinetic properties in man is limited. Urokinase administered by intravenous infusion is rapidly cleared by the liver with an elimination half-life for biologic activity of 12.6 ± 6.2 minutes and a distribution volume of 11.5 L. Small fractions of the administered dose are excreted in bile and urine. Although the pharmacokinetics of exogenously administered urokinase have not been characterized in patients with hepatic impairment, endogenous urokinase-type plasminogen activator plasma levels are elevated 2- to 4-fold in patients with moderate to severe cirrhosis.[1] Thus,

reduced urokinase clearance in patients with hepatic impairment might be expected.

Intravenous infusion of Kinlytic™ in doses recommended for lysis of pulmonary embolism is followed by increased fibrinolytic activity in the circulation. This effect disappears within a few hours after discontinuation, but a decrease in plasma levels of fibrinogen and plasminogen and an increase in the amount of circulating fibrin and fibrinogen degradation products may persist for 12-24 hours.[2] There is a lack of correlation between embolus resolution and changes in coagulation and fibrinolytic assay results.

Treatment with urokinase demonstrated more improvement on pulmonary angiography, lung perfusion scanning, and hemodynamic measurements within 24 hours than did treatment with heparin. Lung perfusion scanning showed no significant treatment-associated difference by day 7.[3]

Information based on patients treated with fibrinolytics for pulmonary embolus suggests that improvement in angiographic and lung perfusion scans is lessened when treatment is instituted more than several days (e.g., 4 to 6 days) after onset.[4]

INDICATIONS AND USAGE

Kinlytic™ is indicated in adults:

- For the lysis of acute massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments.
- For the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or non-invasive procedures such as lung scanning.

CONTRAINDICATIONS

The use of Kinlytic™ is contraindicated in patients with a history of hypersensitivity to the product (see **WARNINGS** and **ADVERSE REACTIONS**).

Because thrombolytic therapy increases the risk of bleeding, Kinlytic™ is contraindicated in the situations listed below (see **WARNINGS**).

- Active internal bleeding
- Recent (e.g., within two months) cerebrovascular accident
- Recent (e.g., within two months) intracranial or intraspinal surgery
- Recent trauma including cardiopulmonary resuscitation
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diatheses
- Severe uncontrolled arterial hypertension

WARNINGS

Bleeding

The risk of serious bleeding is increased with use of Kinlytic™. Fatalities due to hemorrhage, including intracranial and retroperitoneal, have been reported in association with urokinase therapy.

Concurrent administration of Kinlytic™ with other thrombolytic agents, anticoagulants, or agents inhibiting platelet function may further increase the risk of serious bleeding.

Kinlytic™ therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and other needle puncture sites).

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with Kinlytic™. Venipunctures should be performed as infrequently as possible and with care to minimize bleeding.

Should an arterial puncture be necessary, upper extremity vessels are preferable. Direct pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

In the following conditions, the risk of bleeding may be increased and should be weighed against the anticipated benefits:

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels
- Recent (within 10 days) serious gastrointestinal bleeding
- High likelihood of a left heart thrombus, for example, mitral stenosis with atrial fibrillation
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Pregnancy
- Cerebrovascular disease
- Diabetic hemorrhagic retinopathy
- Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location

When internal bleeding occurs, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy. Should potentially serious spontaneous bleeding (not controllable by direct pressure) occur, the infusion of Kinlytic™ should be terminated immediately, and measures to manage the bleeding implemented. Serious blood loss may be managed with volume replacement, including packed red blood cells. Dextran should not be used. When appropriate, fresh frozen plasma and/or cryoprecipitate may be considered to reverse the bleeding tendency.

Anaphylaxis and Other Infusion Reactions

Post-marketing reports of hypersensitivity reactions have included anaphylaxis (with rare reports of fatal anaphylaxis), bronchospasm, orolingual edema and urticaria (see **ADVERSE REACTIONS: Allergic Reactions**). There have also been reports of other infusion reactions which have included one or more of the following: fever and/or chills/rigors, hypoxia, cyanosis, dyspnea, tachycardia, hypotension, hypertension, acidosis, back pain, vomiting, and nausea. Reactions generally occurred within one hour of beginning Kinlytic™ infusion. Patients who exhibit reactions should be closely monitored and appropriate therapy instituted.

Infusion reactions generally respond to discontinuation of the infusion and/or administration of intravenous antihistamines, corticosteroids, or adrenergic agents.

Antipyretics which inhibit platelet function (aspirin and other non-steroidal anti-inflammatory agents) may increase the risk of bleeding and should not be used for treatment of fever.

Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction and rhabdomyolysis.

Product Source and Formulation with Albumin

Kinlytic™ is made from human neonatal kidney cells grown in tissue culture. Products made from human source material may contain infectious agents, such as viruses, that can cause disease. The risk that Kinlytic™ will transmit an infectious agent has been reduced by screening donors for prior exposure to certain viruses, by testing donors for the presence of certain current virus infections, by testing for certain viruses during manufacturing, and by inactivating and/or removing certain viruses during manufacturing (see **DESCRIPTION**). Despite these measures, Kinlytic™ may carry a risk of transmitting infectious agents, including those that cause Creutzfeldt-Jakob disease (CJD) or other diseases not yet known or identified; thus, the risk of transmission of infectious agents cannot be totally eliminated. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is considered extremely remote.

This product is formulated in 5% albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ImaRx Therapeutics, Inc. [1-866-634-6279].

PRECAUTIONS

General

Kinlytic™ should be used in hospitals where the recommended diagnostic and monitoring techniques are available.

The clinical response and vital signs should be observed frequently during and following Kinlytic™ infusion. Blood pressure should not be taken in the lower extremities to avoid dislodgement of possible deep vein thrombi.

Laboratory Tests

Before beginning thrombolytic therapy, obtain a hematocrit, platelet count, and an activated partial thromboplastin time (aPTT). If heparin has been given, it should be discontinued and the aPTT should be less than twice the normal control value before thrombolytic therapy is started.

Following intravenous infusion of Kinlytic™, before (re)instituting anticoagulants, the aPTT should be less than twice the normal control value.

Results of coagulation tests and measures of fibrinolytic activity do not reliably predict either efficacy or risk of bleeding for patients receiving Kinlytic™.

Drug Interactions

Anticoagulants and agents that alter platelet function (such as aspirin, other non-steroidal anti-inflammatory agents, dipyridamole, and GP IIb/IIIa inhibitors) may increase the risk of serious bleeding.

Administration of Kinlytic™ prior to, during, or after thrombolytic agents may increase the risk of serious bleeding.

Because concomitant use of Kinlytic™ with agents that alter coagulation, inhibit platelet function, or are thrombolytic may further increase the potential for bleeding complications, careful monitoring for bleeding is recommended.

The interaction of Kinlytic™ with other drugs has not been studied and is not known.

Carcinogenicity

Adequate data are not available on the long-term potential for carcinogenicity in animals or humans.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 1,000 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Kinlytic™. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Kinlytic™ is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Kinlytic™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Kinlytic™ should be used with caution in elderly patients.

ADVERSE REACTIONS

The most serious adverse reactions reported with Kinlytic™ administration include fatal hemorrhage and anaphylaxis (see **WARNINGS**).

Bleeding

Bleeding is the most frequent adverse reaction associated with Kinlytic™ and can be fatal (see **WARNINGS**).

In controlled clinical studies using a 12-hour infusion of urokinase for the treatment of pulmonary embolism (**UPET** and **USPET**),[3,5,6] bleeding resulting in at least a 5% decrease in hematocrit was reported in 52 of 141 urokinase-treated patients. Significant bleeding events requiring transfusion of greater than 2 units of blood were observed during the 14-day study period in 3 of 141 urokinase-treated patients in these studies. Multiple bleeding events may have occurred in an individual patient. Most bleeding occurred at sites of external incisions and vascular puncture, with lesser frequency in gastrointestinal, genitourinary, intracranial, retroperitoneal, and intramuscular sites.

Sources of Information on Adverse Reactions

There are limited well-controlled clinical studies performed using urokinase. The adverse reactions described in the following sections reflect both the clinical use of Kinlytic™ in the general population and limited controlled study data. Because post-marketing reports of adverse reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Allergic Reactions

Rare cases of fatal anaphylaxis have been reported (see **WARNINGS**). In controlled clinical trials, allergic reaction was reported in 1 of 141 patients (<1%).

The following allergic-type reactions have been observed in clinical trials and/or post-marketing experience: bronchospasm, orolingual edema, urticaria, skin rash, and pruritus (see **WARNINGS**).

Infusion reaction symptoms include hypoxia, cyanosis, dyspnea, tachycardia, hypotension, hypertension, acidosis, fever and/or chills/rigors, back pain, vomiting, and nausea (see **WARNINGS**).

Other Adverse Reactions

Other adverse events occurring in patients receiving Kinlytic™ therapy in clinical studies, regardless of causality, include myocardial infarction, recurrent pulmonary embolism, hemiplegia, stroke, decreased hematocrit, substernal pain, thrombocytopenia, and diaphoresis.

Additional adverse reactions reported from post-marketing experience include cardiac arrest, vascular embolization (cerebral and distal) including cholesterol emboli (see **WARNINGS**), cerebral vascular accident, pulmonary edema, reperfusion ventricular arrhythmias and chest pain. A cause and effect relationship has not been established.

Immunogenicity

The immunogenicity of Kinlytic™ has not been studied.

DOSAGE AND ADMINISTRATION

Kinlytic™ IS INTENDED FOR INTRAVENOUS INFUSION ONLY.

Kinlytic™ treatment should be instituted soon after onset of pulmonary embolism. Delay in instituting therapy may decrease the potential for optimal efficacy (see **CLINICAL PHARMACOLOGY**).

Dosing

- A loading dose of 4,400 international units per kilogram of Kinlytic™ is given at a rate of 90 mL per hour over a period of 10 minutes. This is followed by a continuous infusion of 4,400 international units per kilogram per hour at a rate of 15 mL for 12 hours.
- Administration of Kinlytic™ may be repeated as necessary.
- A dosing and preparation chart for patients who weigh 37 to 114 kilograms (81 to 250 pounds) is provided as a guide in the Preparation Section that follows below. If the patient is outside of these weights, calculate with dosing information provided above.

Preparation

- The Dose Preparation-Pulmonary Embolism chart is a guidance tool/aid provided for the convenience of the practitioner and may not be complete for every patient.
- Kinlytic™ contains no preservatives. Do not reconstitute until immediately before use. Any unused portion of the reconstituted material should be discarded.
- Reconstitute Kinlytic™ by aseptically adding 5 mL of Sterile Water for Injection, USP, without preservatives, to the vial. **DO NOT USE** Bacteriostatic Water for Injection, USP.
- After reconstitution, the drug product will contain 50,000 international units per milliliter.
- After reconstituting, visually inspect each vial of Kinlytic™ for discoloration and for the presence of particulate material. The solution should be pale and straw-colored; highly colored solutions should not be used. Thin translucent filaments may occasionally occur in reconstituted Kinlytic™ vials, but do not indicate any decrease in potency of this product. To minimize formation of filaments, avoid shaking the vial during reconstitution. Roll and tilt the vial to enhance reconstitution. The solution may be terminally filtered, for example, through a 0.45 micron or smaller cellulose membrane filter.
- No other medication should be added to this solution.
- Prior to infusing, dilute the reconstituted Kinlytic™ with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

The following Dose Preparation-Pulmonary Embolism chart may be used as an aid in the preparation of Kinlytic™ for administration. For administration directions, see next section.

Dose Preparation-Pulmonary Embolism

Patient Weight [kilograms (pounds)]	Total Dose[a] (Loading and Continuous Infusion)	Number of Kinlytic™ Vials Needed for Total Dose	Total Volume of Sterile Water for Injection needed for Reconstitution of Kinlytic™ Vials[b]	+	Volume of 0.9% Sodium Chloride or 5% Dextrose Injection, USP for Infusion (mL)	=	Final Volume (mL) for Loading and Continuous Infusion
37-40 (81-90)	2,250,000	9	45		150		195
41-45 (91-100)	2,500,000	10	50		145		195
46-50 (101-110)	2,750,000	11	55		140		195
51-54(111-120)	3,000,000	12	60		135		195
55-59(121-130)	3,250,000	13	65		130		195
60-64 (131-140)	3,500,000	14	70		125		195
65-68(141-150)	3,750,000	15	75		120		195
69-73 (151-160)	4,000,000	16	80		115		195
74-77 (161-170)	4,250,000	17	85		110		195
78-82 (171-180)	4,500,000	18	90		105		195
83-86 (181-190)	4,750,000	19	95		100		195
87-91 (191-200)	5,000,000	20	100		95		195
92-95 (201-210)	5,250,000	21	105		90		195
96-100 (211-220)	5,500,000	22	110		85		195
101-104 (221-230)	5,750,000	23	115		80		195
105-109 (231-240)	6,000,000	24	120		75		195
110-114 (241-250)	6,250,000	25	125		70		195

[a] Loading Dose + dose administered during 12-hour period.

[b] Each vial is reconstituted with 5 mL of Sterile Water for Injection, USP, without preservatives. (See Preparation.)

Administration

- Kinlytic™ is administered using a constant infusion pump that is capable of delivering a total volume of 195 mL.
- The loading dose of Kinlytic™ admixture (4,400 international units per kilogram) should be delivered at a rate of 90 mL per hour over a period of 10 minutes.
- This is followed by a continuous infusion of 4,400 international units per kilogram per hour of Kinlytic™ at a rate of 15 mL per hour for 12 hours.
- Since some of the Kinlytic™ admixture will remain in the tubing at the end of an infusion pump delivery cycle, the following flush procedure should be performed to insure that the total dose of Kinlytic™ is administered. A solution of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, approximately equal in amount to the volume of the tubing in the infusion set should be administered via the pump to flush the Kinlytic™ admixture from the entire length of the infusion set. The pump should be set to administer the flush solution at the continuous rate of 15 mL per hour.
- No other drug products/solutions may be administered in the same line with Kinlytic™.

Anticoagulation After Terminating Kinlytic™ Treatment

After infusing Kinlytic™, anticoagulation treatment is recommended to prevent recurrent thrombosis. Do not begin anticoagulation until the aPTT has decreased to *less than twice* the normal control value. If

heparin is used, do not administer a loading dose of heparin. Treatment should be followed by oral anticoagulants.

HOW SUPPLIED

Kinlytic™ is supplied as a sterile lyophilized preparation (NDC 24430-1003-1). Each vial contains 250,000 international units urokinase activity, 25 mg mannitol, 250 mg Albumin (Human), and 50 mg sodium chloride. Refrigerate Kinlytic™ powder at 2° to 8°C (36° to 46°F) (See USP).

REFERENCES

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Rx

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KINLYTIC

urokinase injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:24430-1003
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
UROKINASE (UNII: 83G67E21XI) (urokinase - UNII:83G67E21XI)		250000 [iU] in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	25 mg in 5 mL
albumin (human) ()	250 mg in 5 mL

SODIUM CHLORIDE (UNII: 451W47IQ8X)	50 mg in 5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24430-1003-1	5 mL in 1 VIAL		

Labeler - ImaRx Therapeutics, Inc.

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