Kinglytic™ (urokinase for injection) is a thrombolytic agent obtained from human neonatal kidney cells grown in tissue culture. The principal active ingredient of Kinglytic™ 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. Kinglytic™ 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, Kinglytic™ 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 Kinglytic™ vials (see DOSAGE AND ADMINISTRATION).

Kinglytic™ is for intravenous infusion only.

Kinglytic™ is produced from human neonatal kidney cells (see WARNINGS). No fetal tissue is used in the production of Kinglytic™. 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, HDV, 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 viruses during manufacturing, and includes testing for certain current virus infections, by testing for certain viruses in donor sera and by inactivating and/or removing certain viruses during manufacturing (see DESCRIPTION). Despite these measures, Kinglytic™ 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. The 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 Immucor Therapeutics, Inc. [1-866-634-6279].

PRECAUTIONS

General
Kinglytic™ 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 Kinglytic™ infusion.

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.

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

Kinglytic™ 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).

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

CONTRAINDICATIONS

The use of Kinglytic™ 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, Kinglytic™ 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 diathesis
- Severe uncontrolled arterial hypertension

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
Kinglytic™ 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 Kinglytic™ 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 viral infections, and by inactivating and/or removing certain viruses during manufacturing (see DESCRIPTION). Despite these measures, Kinglytic™ 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.
Pregnancy Category B: (UPET and USPET), 3, 5, 6 bleeding resulting in at least of urokinase for the treatment of pulmonary embolism. In controlled clinical studies using a 12-hour infusion WARNINGS). Associated with Kinlytic™ and can be fatal (see WARNINGS). Bleeding subjects. Kinlytic™ should be used with caution in whether they respond differently from younger Clinical studies of Kinlytic™ did not include sufficient Safety and effectiveness in pediatric patients have not been performed. Pediatric Use 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. 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), 1, 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 transfusions 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 have occurred in, 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, oozing ecchymosis, edema, urticaria, skin rash, and urticarial rash (see WARNINGS). Infusion reaction symptoms include hypoxia, cyanosis, dyspnea, tachycardia, hypotension, hypertension, acidosis, fever and/or chills/night sweats, 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, subternal pain, thrombocytopea, and diaphoresis. Additional adverse reactions reported from post-marketing experience include cardiac arrest, pulmonary embolization (cerebral and distal) including cholesterol embolus (see WARNINGS), cerebral vascular accident, pulmonary edema, reperfusion intracranial 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 PREPARATION. DOSAGE AND ADMINISTRATION Kinlytic™ IS INTENDED FOR INTRAVENOUS PREPARATION. 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 likelihood of 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 infusion, at a rate of 90 mL per hour, 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/aids 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. • 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 reconstitute. 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. Administration • Kinlytic™ is administered using a constant infusion pump that is capable of delivering a variable rate of 90 mL per hour for 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 ensure 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 1. Sato S. et al. Elevated Urokinase-Type Plasminogen Activator Plasma Levels Are Associated With Deterioration of Liver Function But Not With Hepatocellular Carcinoma. J Gastroenterology; 1994; 29:745-751. 2. Bell WR. Thrombolytic Therapy: A Comparison Between Urokinase and Streptokinase. Sem Thromb Hemost; 1975; 2:1-13. 3. Sasahara AA, Hyers TM, Cole GM, et al. The Urokinase Pulmonary Embolism Trial. Circulation. 1973; 47 (suppl. 2):I-108. 4. Daniels LB, Parker JA, Patel SR, Grodstein F, Goldhaber SZ. Relation of Duration of Symptoms With Response to Thrombolytic Therapy in Pulmonary Embolism. Am J Cardiol. 1997; 80:184-188. 5. Urokinase Pulmonary Embolism Trial Study Group: Urokinase-Streptokinase Embolism Trial. JAMA. 1974; 229:1016-1013. 6. Sasahara AA, Bell WR, Simon TL, et al. The Phase II Urokinase-Streptokinase Pulmonary Embolism Trial. Thrombos Diathes Haemorrh (Stuttg). 1975; 33:464-476.