Fibrinolytic Enzyme Preparation

UROKINASE- Green Cross Inj. 60,000 IU

Urokinase is a plasminogen activator present in traces within human urine.

UROKINASE-Green Cross Inj. 60,000 IU, prepared by isolation and purification from human urine while still intact, has a minor antigenicity and toxicity and has been broadly used as a remedy for various types of thrombosis and embolism. Thus, its usefulness has been confirmed.

COMPOSITION

UROKINASE-Green Cross Inj. 60,000 IU is a sterile lyophilized preparation of urokinase isolated and purified from fresh human urine. Each vial contains 60,000 IU of urokinase and also contains 40mg of human serum albumin as inactive ingredient.

INDICATIONS

Treatment of the following thrombotic-occlusive diseases:

- Cerebral thrombosis (within 5 days after the onset of symptoms, and without hemorrhage detectable by computed tomography)
- Peripheral arterial-venous occlusion (within 10 days after the onset of symptoms)

DOSAGE AND ADMINISTRATION

Reconstitute the contents of one vial with 10 mL of physiological saline and inject intravenously. Preferably instill as an admixture with physiological saline or glucose injection.

[Thrombotic-occulsive diseases]

- Cerebral thrombosis: Administer 60,000 IU once a day for about 7 days.
- Peripheral arterial-venous occlusion: Administer 60,000 to 240,000 IU on first day of treatment followed by tapered doses for about 7 days.

WARNINGS

Serious hemorrhagic cerebral infarction in patients receiving the drug has been reported. The diagnosis of cerebral thrombosis should be fully confirmed in the patient to be treated in order to avoid use of the drug in patients with cerebral embolisms who are apt to develop hemorrhagic cerebral infarction on thrombolytic therapy

PRECAUTIONS FOR USE

(1) General precautions

1) Hemorrhagic cerebral infarction may occur in patients receiving this product. Therefore, the patient should be thoroughly examined by means of computed tomography and clinical assessments be made with regard to the status of onset of the symptoms and clinical manifestations, and the use of this product should be avoided in patients with a possibility of cerebral embolism or with a risk of bleeding.
2) Since the use of this product is accompanied by an increased risk of hemorrhage, it must be ascertained beforehand whether hemorrhage is present or not, and patients receiving this product should be carefully monitored frequently by hematologic examinations such as blood coagulability (bleeding time, prothrombin time, and the like) and observed for clinical signs. If intracerebral hemorrhage is suspected, urokinase therapy should be withdrawn immediately. Intracerebral hemorrhage is ascertained by means of computed tomography as a rule. If CT is not available, this product should be administered only when findings from a cerebrospinal fluid examination and observation of clinical signs and symptoms indicate absence of any hemorrhagic lesion.

(2) Contraindications

1) Patients for whom hemostatic management is difficult: intracranial hemorrhage, hemoptysis, retroperitoneal hemorrhage and the like.
2) Patients having undergone intracranial or spinal surgery or with such injury (in the last 2 months).
3) Patients with aneurysm.
4) Patients with serious disturbances of consciousness.

(3) Contraindications as a general rule

This product is contraindicated in the following patients, as a general rule. If essential, however, it can be administered with caution.

1) Patients with atrial fibrillation (particularly with mitral stenosis), patients with infective endocarditis, patients with old myocardial infarction, and patients with a prosthetic valve.
2) Patients with neurological signs and symptoms of stroke which became complete instantaneously.

(4) Careful Administration

1) Patients with hemorrhage: under surgical treatments such as operations (including hepatic, renal biopsies), hemorrhagic oculopathy such as diabetic hemorrhagic retinopathy, hemorrhage of the digestive tract, hemorrhage of the urinary tract, abortion or premature delivery, immediately after child delivery, during menstruation, and the like.
2) Patients with possible hemorrhage: ulcers of the digestive tract, diverticulitis of the digestive tract, colitis, serious hypertension, active tuberculosis, a history of intracranial hemorrhage and the like.
3) Patients receiving treatment with anticoagulants.
4) Patients with serious hepatic or renal disturbances.
5) Patients with intractable hypocoagulability: coagulation factor deficiency, thrombocytopenia, and the like.
6) Elderly patients (Refer to the “Administration to elderly patients” section).
7) Patients with a history of hypersensitivity to this product or tissue culture urokinase.

(5) Adverse Reactions

1) **Bleeding tendency:** Patients receiving treatment should be observed cautiously, as cerebral or gastrointestinal hemorrhage, hematuria or gingival hemorrhage may occur rarely. In the event of serious complications such as cerebral or gastrointestinal hemorrhage, treatment should be discontinued and appropriate measures taken.
2) **Shock:** Shock symptoms may occur rarely, so close observation is necessary. In the event of any shock-related signs or symptoms such as lowered blood pressure, dyspnea, intrathoracic distress, disturbed pulse or sweating, therapy should be discontinued and appropriate steps taken.
3) **Hypersensitivity:** Hypersensitivity reactions such as rash and urticaria may occur rarely. Administration should be discontinued if there are such signs.
4) **Hepatic:** Elevated levels of S-GOT or S-GPT may occur rarely.
5) **Gastrointestinal:** Nausea, vomiting and anorexia may occur rarely.
6) **Others:** Fever, chill, headache and malaise may occur rarely.

(6) Administration to elderly patients:

Carefully administer this drug to elderly patients as a risk of hemorrhage may be enhanced.

(7) Use during pregnancy: In view of the fibrinolytic properties intrinsic in urokinase, it seems possible that premature separation of the placenta may occur. Therefore, the product should only be used in pregnant women or women suspected of being pregnant, provided that the expected therapeutic benefits are evaluated to outweigh the possible risks associated with treatment.

(8) Pediatric Use: Safety in children has not been established. (Adequate well-controlled clinical studies in children have not been performed.)

(9) Drug Interactions: The bleeding tendency associated with use of this product may be intensified in combination with the following drugs:

Anticoagulants (warfarin and the like)

Drugs with platelet antiaggregant effects (aspirin, dipyridamole, ticlopidine hydrochloride, and the like).

(10) Cautions in use:

1) Use promptly after reconstitution.
2) When this product is used in admixtures with heparin sodium, the admixture needs to have a pH over 5.0, and when admixed with heparin calcium, the admixture a pH between 5.0 and 7.0 (This product contains human serum albumin as inactive ingredient, so

a precipitate of albumin-heparin conjugates may be formed at pH values under 5.0 and a precipitate of calcium phosphate may be formed in admixtures with heparin calcium at pH values over 7.0).

PHARMACOLOGICAL ACTIONS

Lysis of thrombi-emboli

(1) Plasminogen and fibrinogen are coexistent in the blood, and when fibrin is formed through blood coagulation, plasminogen is incorporated into the fibrin clot. Urokinase acts to convert this plasminogen into plasmin and thereby to dissolve the thrombus.[1-3] The plasmin thus generated within the fibrin clot is not affected by antiplasmins.

(2) According to Ambus et al.[4,5], the plasmin thus activated by urokinase conjugates with anitplasmins and circulates in the blood. Because of its high affinity with fibrin, plasmin is liberated from the antiplasmin-conjugate upon coming into contact with a thrombus, and demonstrates its intrinsic plasmin activity there. Antiplasmins work as a vehicle for plasmin, also serve to inhibit the lysis by plasmin of other plasma proteins (blood coagulation factors and others).

CLINICAL STUDIES

(1) Clinical efficacy

1) Cerebral thrombosis

The use of this product was confirmed by a double blind placebo-controlled study conducted in 126 medical centers nationwide [6]. In open clinical studies, further, "Effective" or better responses were rated to be 50% and "Fairly effective" or better 82.5% [7-9]

2) Peripheral arterial-venous occlusion

The response rates to this product in arterial occlusive diseases amounted to 68.1% when assessed for systemic conditions, 70.2% for subjective symptoms (the vascular system), 65.2% for subjective symptoms (the nervous system), and 57.1% for findings of the soft parts. Moreover, the response rates in venous occlusive diseases amounted to 85.5% for subjective symptoms, 83.0% for objective findings, and 84.0% for perimeter of the extremities. The improvement in angiographic findings was rated to be 25.0% (60.0% rated as "Fairly improved" or better). [10),11)] Further, the efficacy and safety of this product were confirmed by a comparative clinical trial to be superior to those of heparin as control.[12)]

(2) Adverse reactions

Out of a total of 3,794 patients surveyed through the Phase IV studies, 15 patients (0.40%) presented adverse reactions (Table). The primary reactions were hemorrhagic cerebral infarction, gastrointestinal hemorrhage and other hemorrhages (at punctured sites and from wounds).

Table: Incidences of Adverse Reactions

Indications	No. of patients	No. of ADR patients	No. of ADR events	% Incidences (by patients)
Cerebral thrombosis	2,803	11	13	0.39
Peripheral arterial-venous occlusion	991	4	5	0.40
Overall	3,794	15	18	0.40

NON-CLINICAL STUDIES

(1) Toxicity

1) Acute Toxicity [13)]

In acute toxicity studies with mice and rats, even the maximum dose technically injectable (equivalent to 3,000,000 IU/kg of urokinase) did not induce any appreciable abnormalities, and the LD_{50} was estimated to be more than 3,000,000 IU/kg.

2) Subacute toxicity [13)]

In rats given daily 100,000, 30,000 or 10,000 IU/kg of urokinase for 30 consecutive days, no appreciable adverse reactions were observed even with the top dose and hence the maximum toxicologically non-effective dose in rats was estimated to be more than 100,000 IU/kg/day.

(2) Absorption, distribution, metabolism, and excretion in animals.

1) ^{125}I-labeled urokinase at 60,000 IU/50 kg body weight was intravenously administered to beagles, and the changes in blood radioactivity and its eliminations into the urine and feces were measured. In consequence,

(1) The plasma levels of ^{125}I-urokinase decreased rapidly within 1 hour after administration and then decreased gradually following the equation,

-dc/dt=kc (where k: velocity constant)[14)].

2) ^{131}I-urokinase was administered via the tail vein of rats (both sexes), and the distribution of radioactivity in the body and its sequential changes were measured by the whole body autoradiography assay. In consequence,

1. The highest radioactivity was detected in the kidneys shortly after administration, followed by the liver, lungs, heart muscles, and spleen. In these organs except for kidneys, the radio-activities were eliminated rapidly to be cleared after 24 hours.
2. The radioactivity in the kidneys peaked 5 minutes after administration, which persisted for a long time, suggesting that urokinase has an affinity with kidneys.
3. Urokinase was suggested to be eliminated principally into the urine via the kidneys.
4. Male and female rats showed a similar pattern of distribution of urokinase in the organs other than genitals, indicating no intrinsic differences between both sexes.[15)]

DESCRIPTION

(1) Product description

UROKINASE-Green Cross Inj. 60,000 IU is available as a white or pale yellowish lyophilized preparation of urokinase extracted, separated and purified from fresh human urine. This product has been processed by heat treatment at 60°C for 10 hours in order to inactivate pathogenic viruses which may contaminate the source urine. It is freely soluble in 5% glucose injection or in physiological saline and yields a clear injectable solution.

pH: 6.5-7.5 (when reconstituted with physiological saline into 6,000 IU/ml)

Osmotic pressure ratio (to physiological saline): approx. 1 to 2

(2) Physicochemical properties of the active ingredient

(purified urokinase bulk solution)
Nonproprietary name: Urokinase
Molecular weight: 54,000
Description: A clear, colorless liquid.

STORAGE AND HANDLING

(1) Storage: Store at temperatures below 30°C.

(2) Expiration: UROKINASE-Green Cross Inj. 60,000 IU should be used before the expiration date dated on the vial label.

PACKAGE

Box of 10 vials of 60,000 IU

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