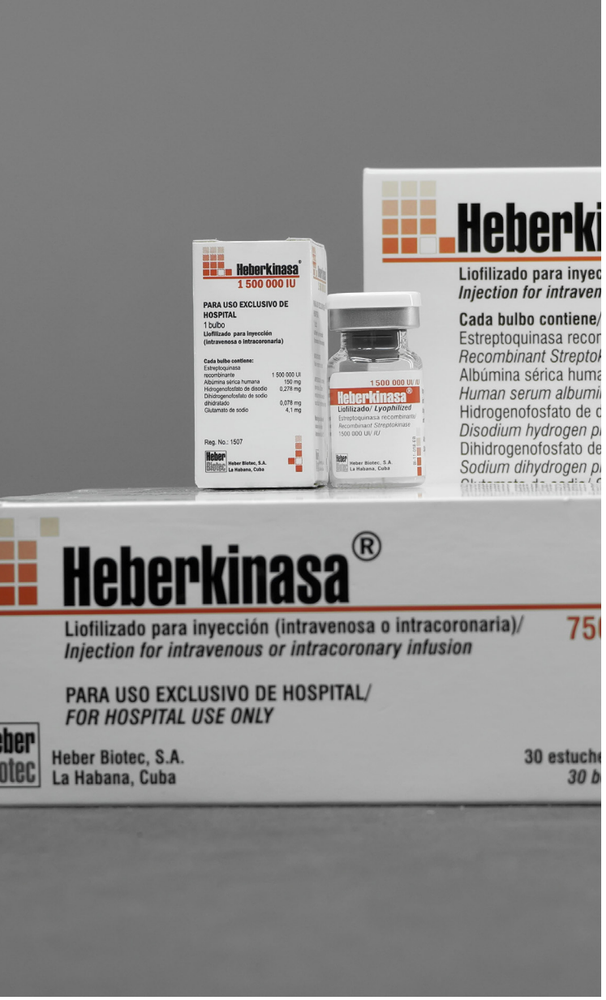

Heberkinasa® should be administered only once through a peripheral vein at a dose of 1 500 000 IU over the course of 60 minutes.

When the product is administered intracoronally through a coronary catheter, the application of a bolus of 20 000 IU is recommended, followed by an infusion of 2000 to 4000 IU per minute for 30 to 90 minutes.

• *Deep venous thrombosis:* For the application of **Heberkinasa®** in this type of condition, the intravenous via locoregional catheter will be used in the axial-subclavian region or in the leg. When the thrombosis is in more than one location, the product will be applied to the most affected limb.

Application should begin as soon as possible after the onset of thrombosis. Patients will receive an initial dose of 250 000 IU within 30 minutes, and a maintenance dose of 100 000 IU per hour in continuous infusion of 24 to 72 hours depending on the time of dissolution of the thrombus.

• *Permanent vascular access thrombosis in patients with end-stage chronic renal failure treated by periodic hemodialysis:* in this condition, **Heberkinasa®** will be administered directly into the arterial portion of the vascular access, by continuous infusion, 1 000 000 IU for a maximum period of 1 hour.

• *Thrombus dysfunction of cardiac valve prostheses:* through a peripheral vein of the upper limbs, 250 000 IU of **Heberkinasa®** diluted in 100 mL of 5 % dextrose or physiological saline solution are administered for 30 minutes. In the event that lysis of the thrombus is achieved, evidenced by clinical and imaging tests, 100,000 IU/h of **Heberkinasa®** should be continued for 72 hours or less.

• *Pulmonary thromboembolism:* 250 000 IU of **Heberkinasa®** diluted in 100 mL of 5 % dextrose or physiological saline solution are administered through a peripheral vein of the upper limbs for 30 minutes. Continue at 100 000 IU per hour for 72 hours or less, if thrombus lysis, as evidenced by the clinic, is achieved.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Increases the risk of severe bleeding in patients receiving corticosteroids, ethacrynic acid or non-acetylated salicylates. The use of antifibrinolytics inhibits the action of thrombolytics. Anticoagulants derived from coumarin or heparin increase the risk of bleeding. Nonsteroidal anti-inflammatory drugs such as acetylsalicylic acid (ASA), indomethacin and phenylbutazone inhibit platelet aggregation and can cause ulceration or gastrointestinal bleeding.

However, in the cases of myocardial infarction, concomitant administration of ASA is indicated since the beneficial effects of **Heberkinasa®** and ASA are added in terms of short-term lethality reduction.

The use of dipyridamole, piperacillin, valproic acid and ticarcillin also inhibits platelet aggregation with increased risk of bleeding.

USE IN PREGNANCY AND LACTATION

The use of **Heberkinasa®** is not recommended in these situations.

EFFECTS ON DRIVING VEHICLES / MACHINERY

Not applicable. It is a medical emergency with hospitalization of the patient. In any case, patients undergoing treatment with **Heberkinasa®** should not drive vehicles or machinery.

OVERDOSE

An overdose of **Heberkinasa®** increases the risk of bleeding.

Center for Genetic Engineering and Biotechnology
Distinctive company of Cuban biotechnology which develops, produces, markets and exports innovative products, for key areas of the biomedical, veterinary, agricultural, aquaculture and industrial sectors, for one health. It has a portfolio of research and development (R&D) projects and products, protected by patents. Its more than 30 products marketed in more than 35 countries, include first and only drugs of its kind, to treat diseases that do not have other effective therapeutic solutions. Several of its medicines are inserted into national programs to offer comprehensive health care. We work with social responsibility and in harmony with the environment.

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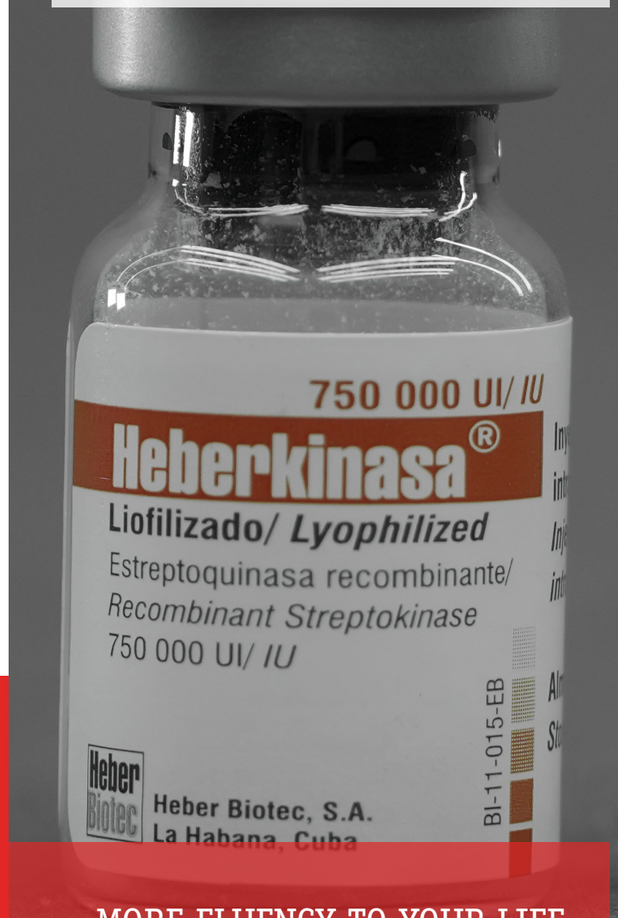
Heberkinasa®

RECOMBINANT STREPTOKINASE



MORE FLUENCY TO YOUR LIFE

Heberkinasa®

Recombinant streptokinase

MORE FLUENCY TO YOUR LIFE

- **HEBERKINASA®** CAUSES RAPID LYSIS OF THE INTRACORONARY THROMBUS.
- IT AVOIDS ISCHEMIC NECROSIS OF THE MYOCARDIUM.
- IT IMPROVES VENTRICULAR FUNCTION AND LIMITS THE INFARCT AREA.
- IT RESTORES VENOUS CIRCULATION AND AVOIDS POST-PHLEBITIS SYNDROME.
- IT REDUCES THE RISK OF PULMONARY EMBOLISM AND FACILITATES THE RAPID REMOVAL OF THE EMBOLUS.

PHARMACEUTICAL FORM

Lyophilized drug for intravenous and intracoronary infusion

STRENGTH

- 750 000 IU of recombinant human streptokinase
- 1 500 000 IU of recombinant human streptokinase

PRESENTATION

- Case per 1 or 30 colourless glass vials with 750 000 IU each
- Case for 1 or 30 clear glass vials with 1 500 000 IU each

COMPOSITION

- Recombinant human streptokinase 750,000 IU; human serum albumin 75 mg; disodium hydrogen phosphate 0.278 mg; 0.078 mg sodium dihydrogen phosphate dihydrated; sodium glutamate 4.1 mg.

- Recombinant human streptokinase 1,500,000 IU; human serum albumin 150 mg; disodium hydrogen phosphate 0.278 mg; 0.078 mg sodium dihydrogen phosphate dihydrated; sodium glutamate 4.1 mg.

SHELF LIFE

- Product not reconstituted: 36 months.
- Reconstituted product: 24 hours.

STORAGE CONDITIONS

- Non-reconstituted product: store at 2 to 8 °C.
- Reconstituted product: store at 2 to 8 °C.

INDICATIONS

The choice of thrombolytic therapy as opposed to other treatments must be evaluated in each patient.

- *Acute myocardial infarction (AMI):* the diagnosis must meet the following characteristics: patients of any age and sex, with pain in the anterior face of the thorax or with a clinical picture suggestive of myocardial ischemia, lasting more than 30 minutes, in the 12 hours preceding the start of treatment, accompanied by ST segment elevation on the electrocardiogram (ECG), of more than 1 mm, in 2 or more derivations of the following: DI, DII, DIII, aVL, or aVF, or more than 2 mm in two or more contiguous precordial leads, or branch block.

The efficacy of **Heberkinasa®** has been demonstrated in clinical trials in the treatment of AMI in 3165 patients. A 28 % reduction in in-hospital mortality is achieved for patients not receiving thrombolytic treatment (approximately 40 lives saved per 1000 patients treated). Intracoronary use, with angiographic control, demonstrated 70 % coronary reperfusion after application of **Heberkinasa®**. The treatment contributes to the reduction in the size of the infarct, as indicated by the reduction in the frequency of heart failure and cardiogenic shock (12.2 vs. 20.5 %, and 1.4 vs. 8.0 %, respectively). These complications are frequently associated with large heart attacks.

- *Deep venous thrombosis:* lysis of the thrombus is achieved in less than 72 hours and the appearance of long-term post-phlebitic syndrome is prevented.

- *Permanent vascular access thrombosis in patients with end-stage chronic renal failure treated by periodic hemodialysis:* the occluded arteriovenous fistula is recovered in 70 % of treated patients.

- *Thrombus dysfunction of cardiac valve prostheses:* 93.3 % success was obtained, avoiding emergency surgery and reducing mortality.

- *Pulmonary thromboembolism:* rapid recovery of cardiopulmonary function and avoidance of vascular bed involvement.

CONTRAINDICATIONS

Heberkinasa® is contraindicated in active hemorrhages, brain tumor or stroke, recent thoracic surgery, severe uncontrolled hypertension, dissecting aneurysm, cerebrovascular disease, subacute bacterial endocarditis, diabetic hemorrhagic retinopathy, recent severe or minor trauma, sepsis at the site of the thrombus or near the thrombus, pregnancy and lactation. Also, in active tuberculosis, kidney and/or liver failure.

It is contraindicated in the preceding year to allergy to **Heberkinasa®** or with a history of allergy to **Heberkinasa®**.

The risk-benefit ratio should be evaluated in any clinical setting where there is a risk of bleeding or where it would be difficult to control due to its location.

PRECAUTIONS

In patients 75 years or older, the risk of cerebral hemorrhage increases. It should be administered with great caution during the first 10 days after delivery due to the increased risk of bleeding. To minimize the risk of bleeding during thrombolytic therapy, the patient should be in bed, absolute rest, avoiding any manipulation or movement, invasive procedures (biopsies) or intramuscular injections that are not essential. If heparin was being treated, it should be discontinued. The resistance to lysis of the thrombus increases with its age, so the therapy should be carried out as soon as possible after clinical symptoms appear.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

It should only be used under optional prescription. The treatment must be carried out by specialized personnel, who have the necessary diagnostic facilities, as well as sufficient experience in the thrombolytic therapy of IMA and other thrombotic diseases. This medicine may only be used until the expiration date indicated on the case.

After reconstitution, the solution can be stored between 2 and 8 °C for 24 hours, without implying loss of activity. After that reconstitution period, the solution should not be used.

UNDESIRABLE EFFECTS

Over 3000 patients were included in the clinical trials with **Heberkinasa®**.

Proportion of patients with adverse events > 1 %:

Adverse events	Frequency (%)	Adverse events	Frequency (%)	Adverse events	Frequency (%)
Arrhythmia	47.8	Others	2.2	Anaphylactic shock	0.8
Arterial hypotension	24.0	Myocardial reinfarction	2.4	Sudden death	1.6
Shaking chills	12.7	Nausea	2.1	Cardiogenic shock	1.4
Tremor	12.0	Stroke (AVE)	1.1	Bleeding	3.2
Angina pectoris	10.0	Hemorrhagic	0.3	Higher	0.9
Vomiting	7.7	Ischemic	0.6	Less	2.3
Fever	7.3	Undefined	0.2	Cardiac wall rupture (confirmed by necropsy)	1.8
Angioneurotic edema	0.2	Allergy	3.2		

DOSAGE AND MODE OF ADMINISTRATION

Reconstitution and preparation of the medicine

The reconstitution and dilution of the medicine, when it is going to be applied by intravenous infusion, is made with 5 mL of water for injection, trying to direct the liquid towards the walls of the bulb, which must be carefully turned to avoid the formation of foam. The concentrated solution obtained is aseptically transferred to an infusion bottle of adequate volume, according to the patient's needs. The most appropriate solutions are 0.9 % sodium chloride or 5 % dextrose. No other products should be added to this preparation.

- *Acute myocardial infarction:* **Heberkinasa®** administration should begin as soon as possible, never more than 12 hours after the onset of symptoms, either intravenously or directly intracoronally. In systemic treatment,