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Biocon

Recombinant Streptokinase for Injection 1, 500,000 IU

MYOKINASE®
मायोकाईनेस

Composition:
Each vial contains
Recombinant streptokinase.....1,500,000 IU
(Stabilized pure streptokinase is derived from the culture filtrate of beta-haemolytic streptococci group C. Streptokinase is a single-chain polypeptide of 47285 Da (414 amino acids) expressed in E.coli as an intracellular soluble product).

Pharmaceutical form:
White to off-white Odourless solid.

Lyophilized powder: To be reconstituted with 5ml of sterile physiological saline or 5% dextrose.

For intravenous administration.
Single dose use only.

Indications:
MYOKINASE® is indicated in the management of
- Acute myocardial infarction
- Pulmonary embolism
- Deep vein thrombosis (DVT)

Dosage and method of administration
Acute Myocardial Infarction:
I.V. infusion - Administer streptokinase as soon as possible after symptom onset (greatest benefit when administered within 4 hr, but statistically significant benefit has been reported up to 24 hr). Infuse a total dose of 1,500,000 within 60 min.

Intracoronary infusion - Administer 20,000 IU by bolus followed by 2000 IU/min for 60 min (Total dose, 140,000 IU).

Deep Vein Thrombosis and Pulmonary Embolism:
I.V. infusion- Streptokinase, treatment should be instituted as soon as possible after onset of the thrombotic event, preferably within 7 days. A loading dose of 250,000 IU infused into a peripheral vein over 30 minutes has been found appropriate in over 90% of patients. If thrombin time or any parameter of lysis after 4 hr of therapy is not significantly different from the normal control level, discontinue streptokinase because excessive resistance is present. Dose and duration of therapy (following the loading dose of 250,000 IU/30 min) for Pulmonary Embolism 100,000 IU/hr for 24 hr (72 hr if concurrent for DVT is suspected); DVT 100,000 IU/hr for 72 hr; arterial thrombosis or embolism 100,000 IU/hr for 24 to 72 hr.

Administration
- Reconstitute the MYOKINASE® vial contents with 5ml sterile physiological saline or Dextrose (5%), directing the diluent along the side of vial rather than into the drug powder.
- Avoid shaking (shaking may cause foaming) and gently roll and tilt the vial to reconstitute.
- Withdraw the entire reconstituted contents of the vial; slowly dilute further in 50- 200 mL physiological saline or Dextrose 5%.
- Infuse intravenously over a period of one hour.

Pharmacological Properties:
Pharmacodynamic properties
Pharmacotherapeutic group: Streptokinase (antithrombotic agents, enzymes). ATC code: B01A D01
MYOKINASE® is a highly purified streptokinase derived from β haemolytic streptococci of group C. The activation of the endogenous fibrinolytic system is initiated by the formation of a streptokinase-plasminogen complex.

This complex possesses activator properties and converts plasminogen into the proteolytic and fibrinolytic active, plasmin. The more plasminogen that is bound within this activator complex, the less plasminogen is left to be converted into its enzymatically active form. Therefore, high doses of streptokinase are associated with a lower bleeding risk and vice versa.

After intravenous administration and neutralisation of the individual antistreptokinase-antibody titer, streptokinase is immediately available systemically for activation of the fibrinolytic system.

Streptokinase has a very short half-life. The first rapid clearance from the plasma is due to the formation of the complex between streptokinase and streptokinase antibody. This complex is biochemically inert and is cleared rapidly from the circulation. Once the antibody has been neutralised, the streptokinase activates plasminogen as described above.

Clinical trial data
A Randomized, Comparative, Multicentric study was performed to evaluate safety and efficacy of recombinant streptokinase of Biocon Ltd. MYOKINASE® with Streptase® in patients with acute myocardial infarction. A total of 62 subjects were recruited into the trial, and randomized 1:1 to receive MYOKINASE® (n=31) or Streptase® (n=31). Clinical and demographic profiles were similar in both the groups. The clinical trial established the equivalence of Streptase® with MYOKINASE® in efficacy as defined. A comparison of ST segment resolution ≥50% in both the groups by ECG evaluation at 90 minutes after thrombolytic therapy met the pre defined equivalence limit of (-25%, 25%) (Observed 90% CI for the difference between the two groups was -21.05 %, 14.6%). The percentages of subjects who achieved ≥50% reduction in ST segment elevation in the MYOKINASE® arm (50%) and Streptase® arm (58.08%) were not different statistically. In terms of CK-MB ratio post/pre-thrombolysis the lower limit of 90% CI for the difference between the two groups was below the pre-defined limit of -25% (Observed 90% CI was -28.56, 11.14).

There was no evidence to conclude that the two treatments are significantly different in abrupt resolution of chest pain and reduction in chest pain of ≥50% (MYOKINASE® -19.35% abrupt resolution, 90.3% reduction of ≥50%; Streptase® - 6.7% abrupt resolution, 87.1% reduction of ≥50%). In-hospital mortality rates of 8.33% and 5.26% were observed in the MYOKINASE® and Streptase® groups respectively (not statistically different).

The incidence of adverse events was similar and not statistically different between the two study groups. In all, 6 cardiac disorders were reported in the MYOKINASE® group, while 5 cardiac disorders were reported in the Streptase® group.

Pharmacokinetic properties
Due to the high degree of affinity and rapid reaction between streptokinase and antistreptokinase-antibodies, which may be present in the patient's blood, low quantities of streptokinase are eliminated from blood with a half-life of 18 minutes. The elimination half-life of streptokinase based on activator formation is about 80 minutes.

Peak fibrinolytic activity is found in the blood about 20 minutes after dosing. Activity is detected in the urine 2 hours after dosing.

The major part of streptokinase is degraded to peptides and eliminated by the kidneys.

Contraindications:
Streptokinase must not be used in case of severe allergic reactions to the product.
Because of the increased risk of haemorrhage under thrombolytic therapy streptokinase must not be given in the following situations:
- Existing or recent internal haemorrhages
- All forms of reduced blood coagulability, in particular spontaneous fibrinolysis and extensive clotting disorders
- Recent cerebrovascular insults, intracranial or intraspinal surgery
- Intracranial neoplasm.
- Arteriovenous malformation or aneurysm.
- Known neoplasm with risk of haemorrhage.
- Acute pancreatitis.
- Uncontrollable hypertension with systolic values above 200 mm Hg and/or diastolic values above 100 mm Hg or hypertensive retinal changes grades III/IV.
- Recent implantation of a vessel prosthesis.
- Simultaneous treatment with oral anticoagulants (INR >1.3).
- Severe liver or kidney damage.
- Known haemorrhagic diathesis.

Special warnings and special precautions for use:
Individual benefit/risk assessment
The risk of therapy in case of life-threatening thromboembolic events, in particular that of haemorrhages, must be weighed against the anticipated benefit in cases such as:
- recent severe gastrointestinal bleeding, e.g. active peptic ulcer
- risk of severe local haemorrhage, e.g. in case of aortography by lumber route
- recent trauma and cardiopulmonary resuscitation
- invasive operations, e.g. recent intubation
- puncture of non-compressible vessels, intramuscular injections
- recent delivery, abortion
- diseases of the urinogenital tract with existing or potential sources of bleeding (implanted bladder catheter)
- known septic thrombotic disease
- severe atherosclerotic vessel degeneration, cerebrovascular diseases
- cavernous pulmonary diseases, e.g. open tuberculosis
- mitral valve defects or atrial fibrillation

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Antistreptokinase antibodies
Because of the increased likelihood of resistance due to antistreptokinase antibodies, repeat treatment with MYOKINASE® or streptokinase containing products may not be effective if administered more than 5 days, particularly between 5 days and 12 months after initial treatment.

Likewise, the therapeutic effect may be reduced in patients with recent streptococcal infections such as streptococcal pharyngitis, acute rheumatic fever and acute glomerulonephritis.

Infusion rate and corticosteroid prophylaxis
At the beginning of therapy, a fall in blood pressure, tachycardia or bradycardia (in individual cases reaching as far as shock) is commonly observed. Therefore, at the beginning of therapy the infusion should be performed slowly.

Corticosteroids can be administered prophylactically to reduce the likelihood of infusion-related allergic reactions.

Pre-treatment with heparin or coumarin derivatives
If the patient is under active heparinization, it should be neutralised by the administration of protamine sulphate before the start of the thrombolytic therapy. The thrombin time should not be more than twice the normal control value before thrombolytic therapy is started. In patients previously treated with coumarin derivatives, the INR (International Normalized Ratio) must be less than 1.3 before starting the streptokinase infusion.

Simultaneous treatment with acetylsalicylic acid
A positive, mutually reinforcing effect of acetylsalicylic and streptokinase on the life expectancy of patients with suspected myocardial infarction has been reported. The administration of acetylsalicylic acid should commence prior to the streptokinase therapy and be continued for at least one month.

Drug-drug interactions:
The potential for an additive hypotensive effect should be borne in mind when streptokinase therapy is combined with antihypertensive agents, such as βblockers and glyceryl trinitrate.

Until information regarding the interaction between streptokinase and tissue plasminogen activator (tPA) is available, special care should be taken if such a combination is considered.

There is an increased risk of hemorrhage in:
Patients previously receiving heparin or coumarin derivatives. The effect of heparin can, however, be rapidly neutralized by administering protamine sulfate. In the case of prior treatment with coumarin derivatives, the Quick value must be more than 50% before the beginning of lysis.

Patients receiving simultaneous treatment with platelet aggregation inhibitors, e.g., phenylbutazone, dipyridamole and nonsteroidal anti-inflammatory drugs.

(NSAIDs). Patients receiving simultaneous or previous treatment with dextrans.

Pregnancy and lactation:
Treatment of pregnant patients with streptokinase is not recommended because safety and effectiveness have not been established, and should be given to pregnant women only if clearly needed.

It is not known whether it is excreted in human milk so should be used with caution in lactating mother. Breast milk should be discarded during the first 24 hours following thrombolytic therapy.

Adverse effects:
Bleeding associated with streptokinase therapy can manifest as minor bleeding or major internal bleeding.

Less serious spontaneous bleeding includes superficial hematoma, hematuria, and hemoptysis. Severe spontaneous bleeding occurs less frequently and includes cerebral (e.g., intracranial bleeding or stroke). genitourinary, retroperitoneal bleeding, and GI bleeding. In rare instances, fatalities have been reported. Hypotension, sometimes severe, has occurred in 10% of patients.

Fever and shivering, occurring in 14% of patients, are the most commonly reported allergic reactions associated with streptokinase. Anaphylactic and anaphylactoid reactions ranging in severity from minor breathing difficulty to bronchospasm, periorbital or angioedema have been observed rarely.

Other allergic reactions include urticaria, pruritus, flushing, nausea, headache, arthralgia, and myalgia.

Delayed hypersensitivity reactions such as vasculitis and interstitial nephritis have been reported. Anaphylactic shock is very rare occurring in ≤0.1% of patients.

Reperfusion of coronary arteries following the lysis of coronary thrombi by streptokinase can cause atrial or ventricular arrhythmias including accelerated idioventricular rhythm, premature ventricular contractions (PVCs), junctional rhythm, atrial fibrillation, ventricular tachycardia, sinus tachycardia, or sinus bradycardia.

Patients receiving streptokinase therapy should be closely observed for possible cardiac arrhythmias.

Other rare adverse events are recurrence or development of pulmonary embolism, noncardiogenic pulmonary edema and acute myocardial infarction, acute cerebrovascular accident, and acute renal failure resulting from cholesterol microembolization in a renal graft have been reported rarely during streptokinase therapy.

Antistreptokinase antibody formation may result in resistance if streptokinase is administered between 5 days and 12 months of prior steptokinase or anistreplase administration or streptococcal infections.

Overdose:
Long-term overdosage of streptokinase may induce the risk of re-thrombosis by prolonged decrease of plasminogen.

Preclinical safety data:
According to published information Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

Pharmaceutical Particulars:
List of excipients
Human albumin
Polygeline
L-Glutamic Acid Monosodium Salt Monohydrate.

Incompatibilities:
Other drugs should not be added to the infusion solution.

Storage and precautions:
MYOKINASE® should be stored between +2°C and +8°C in a sealed container, protected from light.

The reconstituted preparation can be stored between +2°C and +8°C for 24 hours.

Shelf life:
Please refer to expiry date on label/carton.

Presentation:
MYOKINASE® is available in vial as lyophilized powder for injection containing 1,500,000 IU of Recombinant Streptokinase.

Manufactured by :
Biocon Limited
Biocon Special Economic Zone
Plot No. 2-4, Phase IV,
Bommasandra-Jigani Link Road,
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To report adverse events and/or product complaints visit our website www.biocon.com or call toll free No: 1800 102 9465 or e mail us at drugsafety@biocon.com