STK® Injection

Streptokinase 1 500 000 IU

Presentation

STK® Injection: Each vial contains 1 500 000 IU stabilized pure streptokinase as lyophilized powder.

Description

Streptokinase is highly purified Streptokinase obtained from the culture filtrate of beta-haemolytic Streptococci of group C. Streptokinase acts with plasminogen to produce an 'activator complex' that converts plasminogen to the proteolytic enzyme, plasmin. The more plasminogen bound within this 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 low doses of Streptokinase are associated with a higher bleeding risk.

Indications and Uses

- Acute Evolving Myocardial Infarction
- Acute Massive Pulmonary Embolism
- Deep Vein Thrombosis
- Arterial Thrombosis or Embolism
- Arteriovenous Cannulae Occlusion

Dosage and Administration

Streptokinase should be given either by intravenous infusion or by injection close to the site of occlusion (intra-arterially). The route of administration, dosage and duration of therapy will depend on the indication.

Acute Evolving Myocardial Infarction:

Streptokinase should be given as soon as possible after onset of symptoms. The greatest benefit in terms of mortality reduction is observed when the high dose, short term lysis treatment is instituted within 4 hours of onset of symptoms. The agent should not be administered to patients with symptoms greater than 6 hours duration of myocardial pain or transmural ischaemia.

Pulmonary Embolism, Deep Vein Thrombosis & Arterial Thrombus or Embolism:

Streptokinase treatment should be instituted as soon as possible after onset of the thrombotic event, preferably within 7 days.

Arteriovenous Cannulae Occlusion:

Instil 250 000 IU Streptokinase in 2 mL of solution into each occluded limb of the cannula slowly.

Dosage Scheme

	Initial Dose	*Maintenance Dose*	*Long-term control/Anti-coagulant Therapy*
A. IV ADMINISTRATION High dose, short-term lysis for			
Acute Myocardial infarction	Single dose of 1 500 000 IU over 30-60 min. Aspirin may also be instituted at the discretion of the physician.	If reocclusion occurs within 5 days of initial dose a second dose may be given.	No laboratory tests are necessary before or during Streptokinase therapy. Aspirin may be continued at the discretion of the physician. Additional anticoagulant therapy may be given at the discretion of the treating physician.
Long-term lysis for			Prothrombin time (PTT) should be tested from the 16th hour after commencement of STK infusion. Adequate anticoagulation protection is achieved if PTT is 2 to 4 times normal.
Deep Vein Thrombosis Arterial Thrombus Pulmonary Embolism	250 000 IU over 30 min	100 000 IU/hr for 24-120 hrs depending on location, extent of occlusion and clinical improvement	If PTT is < twice normal, give heparin at a rate of 500 to 800 IU/hr. If PTT is > 2 to 4 times normal, double the dose of Streptokinase for several hours. If dose-regulation fails at greatly prolonged PTT, discontinue Streptokinase. If PTT shows tendency towards normal values, give heparin 500 - 800 IU/hr simultaneously with continued maintenance dose of Streptokinase. Continue heparin until PTT is within the normal therapeutic range

B. LOCAL ADMINISTRATION

Intracoronary infusion for Acute Myocardial infarction	20 000 IU bolus (up to 200 000 IU has been given as an initial bolus).	2 to 4 000 IU/ minute for 30-90 minutes (average 60 minutes)	
Other intra-arterial application	1 to 2 000 IU at 3 to 5 min intervals up to 3 hours		Heparin treatment is recommended after Streptokinase therapy to prevent rethrombosis.
Arterio venous cannulae occlusion	Instil 250 000 IU in 2 mL solution slowly into occluded limb, clamp off cannula limbs for 2 hours		After treatment, aspirate contents of infused cannulae limb(s), flush with saline and reconnect cannulae.

Reconstitution and Dilution:
The protein nature and lyophilized form of Streptokinase, require careful reconstitution and dilution. The following reconstitution and dilution procedures are recommended for vials & infusion bottles:

1. Slowly add 5 mL Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to the Streptokinase vial directing the diluent at the side of the vacuum-packed vial rather than into the drug powder.
2. Roll and tilt the vial gently to reconstitute. Avoid shaking. (Shaking may cause foaming.) (If necessary, total volume may be increased to a maximum of 50 mL in plastic containers and the infusion pump rate should be adjusted. To facilitate setting the infusion pump rate, a total volume of 45 mL, or a multiple thereof, is recommended.
3. Withdraw the entire reconstituted contents of the vial; slowly and carefully dilute further to a total volume as recommended. Avoid shaking and agitation on dilution.
4. When diluting the 1 500 000 IU infusion bottle (50 mL), slowly add 5 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, directing it at the side of the bottle rather than into the drug powder. Roll and tilt the bottle gently to reconstitute. Avoid shaking as it may cause foaming. Add an additional 40 mL of diluent to the bottle, avoiding shaking and agitation. (Total volume = 45 mL). Now administer by infusion pump.
5. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. (Human albumin may impart a slightly yellow color to the solution)
6. As Streptokinase contains no preservatives, it should be reconstituted immediately before use. The solution may be used for direct intravenous administration within eight hours following reconstitution if stored at 2 -8 °C (36 -46 °F).
7. Do not add other medication to the container of Streptokinase.
8. Unused reconstituted drug should be discarded.

Side-effects
The following adverse reactions are based on experience from clinical trials and on post marketing experience of Streptokinase.

General disorders

Common: Headache and back pain, muscle pain (including myalgia), chills and/or fever as well as asthenia/malaise.

Haemorrhage and bleeding

Common: Haemorrhages at invaded or disturbed sites, including the injection site, and ecchymoses. Gastrointestinal or genitourinary bleedings (including aggravation of menstrual bleeding), epistaxis.

Uncommon: Intracranial haemorrhages with their complications and possible fatal outcome, retinal haemorrhages, severe haemorrhages (also with fatal outcome) including liver haemorrhages, retroperitoneal bleedings, splenic rupture. Blood transfusions are rarely required.

Immune system disorders

Very common: Development of antistreptokinase antibodies
Common: Allergic-anaphylactic reactions such as rash, flushing, itching, urticaria, angioneurotic oedema, minor breathing difficulty, periorbital swelling, bronchospasm or hypotension.

Nervous system disorders

Rare: Neurologic symptoms (e.g., dizziness, confusion, paralysis, hemiparesis, agitation or convulsion) in the context of cerebral haemorrhages or cardiovascular disorders with hypoperfusion of the brain.

Cardiac complication and vascular disorders

Very common: Hypotension, heart rate and rhythm disorders, angina pectoris.
Common: Recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema.
Uncommon: Cardiac arrest (leading to respiratory arrest), mitral insufficiency, pericardial effusion, cardiac tamponade, myocardial rupture, pulmonary or distal embolism.

Respiratory disorders

Very rare: Non-cardiogenic pulmonary oedema after intracoronary thrombolytic therapy in patients with extensive myocardial infarction.

Gastrointestinal disorders

Common: Nausea, diarrhoea, epigastric pain and vomiting.

Precautions

Because of the increased likelihood of resistance, due to antistreptokinase antibodies, retreatment with Streptokinase or Streptokinase-containing products may not be effective if administered between five days and twelve months of prior Streptokinase administration or Streptococcal infections, such as Streptococcal pharyngitis, acute rheumatic fever or acute glomerulonephritis secondary to a Streptococcal infection.

In principle, no thrombolytic treatment should be commenced before the 10th postoperative day. However, in cases of pulmonary embolism, the indication for earlier treatment may be very strong and after careful consideration of all the risks, Streptokinase may be given before the tenth postoperative day. The danger of bleeding from the operative area must, of course, be taken into account.

The danger of haemorrhage is increased by simultaneous or previous treatment with anticoagulants (e.g., Heparin) or substances which inhibit platelet formation or function. If the patient is under active heparinisation, it should be neutralised by the administration of protamine sulphate before the start of thrombolytic therapy.

Repeated Administration

After administration of Streptokinase, the titre of antistreptokinase antibodies begins to rise after approximately one week, reaching a peak at 2 to 3 weeks and remains elevated for 8 to 12 months. Because of the increased likelihood of resistance, Streptokinase may not be effective if given during this period.

Drug-drug interactions

There is an increased risk of haemorrhage in patients simultaneously or previously receiving anticoagulants (such as Heparin or Coumarin derivatives) or drugs which inhibit platelet formation or function (e.g., Platelet aggregation inhibitors, Dextrans, Phenylbutazone, Dipyridamole, Non-steroidal anti-inflammatory drugs). The effect of Heparin can be neutralized rapidly by administration of Protamine Sulphate. The Thrombin time (TT) should not be more than twice the normal control value before thrombolytic therapy is started. In the case of prior treatment with coumarin derivatives, the International Normalized Ratio (INR) must be less than 1.3 before starting Streptokinase infusion.

Combination of Streptokinase with Aspirin for treatment of Myocardial infarction

Study showed a significant benefit to patients treated with these two agents after acute myocardial infarction. Mortality (both short and longer term) was reduced in these patients to a greater extent than in those treated with either agent alone.

Unless contraindicated, the concomitant use of Acetylsalicylic acid (ASA, Aspirin), starting prior to Streptokinase infusion and continued for one month thereafter may be instituted at the discretion of the physician. The benefit of combination therapy should therefore be weighed against the risk of increased haemorrhage.

Anticoagulation treatment following Streptokinase

Following high dose (1.5 million IU), short term treatment with Streptokinase, for acute myocardial infarction, the use of subsequent anticoagulant treatment has not yet been shown to be of unequivocal benefit. Therefore, in this situation, the use of anticoagulants should be decided by the physician.

Contraindication

As thrombolytic therapy increases the risk of bleeding, Streptokinase, administered either systemically or locally, is contraindicated in the following situations:

- Existing or recent haemorrhage and haemorrhagic diathesis (with the exception of consumption coagulopathy)
- Potential for internal bleeding (e.g., peptic ulcer, ulcerative colitis, diverticulitis or visceral tumours)
- All forms of reduced blood coagulability, in particular spontaneous fibrinolysis and extensive clotting disorders
- Recent (within 2 months) cerebrovascular accident, recent (within 10 days) facial or head trauma, intracranial or intraspinal surgery, known intracranial neoplasm and all known neoplasms with risk of haemorrhage
- Invasive operations, e.g., recent organ biopsy, invasive diagnostic procedure, recent implantation of a vessel prosthesis, long-term traumatic closed-chest massage or other recent surgery (until the 6th to 10th post operative day, depending on the severity of surgical intervention)
- Arteriovenous malformation or aneurysm
- Haemorrhagic diathesis including thrombocytopenia or pronounced hepatic or renal dysfunction
- Severe uncontrolled hypertension (systolic BP > 200 mm Hg, diastolic BP > 100 mm Hg), or hypertensive retinal changes grades III/IV), hypertonic fundus
- Severe liver or kidney damage
- Acute pancreatitis

- Simultaneous treatment with oral anticoagulants (International Normalized Ratio (INR) >1.3)
- Endocarditis or pericarditis (Immediately after streptococcal infections which have produced a high antiStreptokinase titre (acute rheumatic fever, acute glomerulo-nephritis, etc.)
- More than 5 days and less than 12 months since previous Streptokinase therapy.

Use in pregnancy & lactation
Pregnancy category C. It is not known whether Streptokinase is excreted in the breast milk, nor whether it has harmful effects on the newborn. In the absence of further information, it is recommended that breast-feeding be discontinued in women who are to receive Streptokinase.

Pediatric use
Safety & effectiveness in children have not been established.

Overdosage
If uncontrollable bleeding occurs as a result of overdosage, Streptokinase infusion should be ceased immediately. Bleeding can be reversed and blood loss managed effectively with appropriate replacement therapy. Administration of aminocaproic acid or aprotinin may be useful.

Storage
Streptokinase vial should be stored at 2 to 25 ^{o}C. Once reconstituted with physiological saline, the physico-chemical stability has been demonstrated for 24 hours at 2 to 8 ^{o}C. From a microbiological point of view and as Streptokinase 1 500 000 contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 24 hours at 2 to 8 ^{o}C. Keep out of the reach of children.

Commercial pack
STK® Injection: Each box contains 1 vial of 1 500 000 IU stabilized pure streptokinase as lyophilized powder.

Manufactured by
Incepta Pharmaceuticals Ltd
Dhaka, Bangladesh
® Registered Trademark

V.N. 01
STK