

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Streptase Injection 250,000 IU

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Streptokinase 250,000 International Units.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for sterile concentrate

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Streptase is a fibrinolytic agent which may be used for:

The treatment of acute myocardial infarction within 24 hours of the onset of symptoms.

Intravascular dissolution of thrombi and emboli in extensive deep vein thrombosis; pulmonary embolism; acute or sub-acute occlusion of peripheral arteries; central retinal venous or arterial thrombosis.

4.2 Posology and method of administration

Acute myocardial infarction

Streptase should be given by intravenous infusion in 50 - 200ml physiological saline, 5% glucose, 5% fructose, Ringer-lactate solution or Haemaccel as soon as possible after the onset of symptoms.

Systemic administration: A single dose of 1.5 million IU streptokinase should be infused over one hour. No laboratory controls are necessary.

Local application (intra-arterial catheter lysis): Patients with acute myocardial infarction should be given a bolus dose of 20,000 IU streptokinase by intracoronary infusion, followed by a maintenance dose of 2,000-4,000 IU/min for a period of 30-90 minutes.

As usual when performing angiography heparin should be administered, if necessary beforehand, as a safeguard against catheter-induced thrombosis. The success of treatment can be confirmed by angiography. If adequate blood flow continues for more than 15 minutes, the result can be counted as successful and treatment can be terminated.

Adjuvant treatment: Treatment with aspirin (150mg daily) for at least 4 weeks is recommended after streptokinase therapy for acute myocardial infarction. The first dose should be given as soon as possible after the myocardial infarction.

Children: There are no recommendations for the use of Streptase in acute myocardial infarction in children.

Intravascular dissolution of thrombi and emboli

Streptase should be given by intravenous infusion in 50 - 200ml physiological saline, 5% glucose, 5% fructose, ringer-lactate solution or Haemaccel. Since human exposure to streptococci is common, antibodies to streptokinase (streptokinase resistance) are found normally. An initial loading dose to neutralise circulating streptococcal antibodies is followed by a maintenance dose given by slow infusion to continue fibrinolysis.

Loading dose: A dose of 250,000 units of Streptase infused into a peripheral vein over 30 minutes has been found appropriate in over 90% of patients.

Maintenance dose: A maintenance dose infusion of 100,000 units/hour is given following the loading dose. Administer the maintenance dose of 100,000 units per hour for 72 hours for the treatment of deep vein thrombosis, for 24 hours for the treatment of pulmonary embolism (up to 72 hours if concurrent deep vein thrombosis is suspected), for 24-72 hours for the treatment of arterial thrombosis and for up to 12 hours for central retinal thrombosis.

Control of therapy: If the thrombin time of any other parameter of lysis after 4 hours of therapy is less than approximately 1.5 times the normal control value, discontinue Streptase as excessive resistance to streptokinase is present.

Children: In children, in whom it is always advisable to estimate the initial dose by means of the streptokinase resistance test, the recommended maintenance dose per hour is 20 units/ml blood volume.

Patient Monitoring: Before commencing thrombolytic therapy, it is desirable to obtain a thrombin time (TT), activated partial thromboplastin time (aPTT), haematocrit and platelet count to obtain the haemostatic status of the patient. If heparin has been given, it should be discontinued and the TT or aPTT should be less than twice the normal control value before thrombolytic therapy is started.

In patients previously treated with coumarin derivatives, the INR (International Normalised Ratio) should be below 1.7 before starting therapy with streptokinase.

During the infusion, decreases in the plasminogen and fibrinogen level and an increase in the level of fibrin degradation products (FDP) (the latter two serving to prolong the clotting times of coagulation tests) will generally confirm the existence of a lytic state. Therefore therapy can be monitored by performing the TT or aPTT approximately 4 hours after initiation of therapy.

Anticoagulation after terminating intravenous streptokinase therapy: At the end of Streptase therapy, treatment with heparin by continuous intravenous infusion is recommended to prevent recurrent thrombosis. Heparin treatment (without a loading dose) should not begin until the thrombin time has decreased to less than twice the normal control value (approximately 3 to 4 hours). (See manufacturer's prescribing information for proper use of heparin). This should be followed by oral anticoagulation in the conventional manner.

4.3 Contraindications

Systemic administration

Contra-indications to Streptase treatment include all conditions that are likely to be associated with existing or very recent haemorrhage, for example:

- Active internal bleeding.
- Recent cerebrovascular accident.
- Intracranial or intraspinal surgery.
- Known intracranial neoplasm.
- Severe uncontrollable hypertension.
- Uncontrollable clotting disorders.
- Previous severe allergic reactions, including vasculitic purpura, to streptokinase or streptokinase- containing products.

Other contra-indications include:

Existing or very recent haemorrhage associated with:

- all forms of reduced blood coagulability, in particular spontaneous fibrinolysis.
- local lesions with risk of bleeding (e.g. gastrointestinal conditions with existing haemorrhage previous translumbar aortography, puncture of large arteries, intramuscular injections, indwelling catheters or endotracheal tubes).
- recent operations (up to the 6th post-operative day, depending on the extent of the procedure) and recent severe trauma.
- recent abortion or delivery.
- diseases of the urogenital tract with existing or potential sources of bleeding.

Recent streptococcal infections which have produced high anti-streptokinase titres (e.g. acute rheumatic fever, acute glomerulonephritis), or streptokinase therapy more than 5 days and less than 12 months previously.

Subacute bacterial endocarditis.

Severe hypertension with systolic values over 200 mmHg or diastolic values over 100 mmHg or hypertensive retinal changes Grades III/IV.

Severe liver or kidney damage.

Disorders of cerebral blood flow or recent cerebral haemorrhage.

Pulmonary disease with cavitation (e.g. open tuberculosis) or severe bronchitis.

Acute pancreatitis.

Advanced age with suspicion of arteriosclerotic degeneration.

Diagnostic procedures such as lumbar puncture.

Occlusion of the carotid or vertebral arteries.

Septic thrombotic disease.

Pregnancy (see "Precautions").

Local application

When using Streptase for intracoronary lysis the possibility of some systemic effects must be considered, depending on dose level.

The risks of therapy must be weighed against the dangers of the disease.

Usually no success can be expected in myocardial infarction more than 12 hours old.

4.4 Special warnings and precautions for use

Since the anti-streptokinase titre increases after 7-10 days of treatment, and only returns to normal values after 12 months, repeated therapy with streptokinase should only be used with great caution (see 'Contra-indications').

Caution is necessary in patients with mitral valve defects or atrial fibrillation because of the danger of cerebral embolisation from the left side of the heart.

Intramuscular injection should not be given to patients on streptokinase and intravenous injections should be given carefully.

The risks of therapy must be weighed against the dangers of the disease.

In the following conditions streptokinase is unlikely to be effective:

- Deep vein thrombosis more than 14 days old.
- Occlusion of central retinal artery more than 6 - 8 hours old.
- Thrombosis of central retinal vein more than 10 days old.
- Chronic arterial occlusions more than 6 weeks old.

4.5 Interaction with other medicinal products and other forms of interaction

There is an increased risk of haemorrhage in patients who are receiving or who have recently been treated with anticoagulants or any drugs which affect platelet formation or function (e.g. acetylsalicylic acid, allopurinol, anabolic steroids, androgens, dipyridamole, thyroid hormones, volatile oils, quinidine, clofibrilic acid derivatives, phenylbutazone, indomethacin, aryl acetic acid and aryl propionic acid derivatives, tetracyclines, valproic acid, thiouracils and sulphonamides). Simultaneous treatment with dextrans also increases the danger of haemorrhage. The effects of drugs which act upon platelet formation or function should be allowed to subside before starting long-term systemic lysis with Streptase (See "Patient monitoring").

If the patient has been receiving heparin, its effects can be neutralized by giving protamine sulphate. Before starting streptokinase therapy the thrombin time should be less than twice the normal control value.

In patients previously treated with coumarin derivatives, the prothrombin index must not be less than 50% and should have a rising trend before starting streptokinase infusion.

4.6 Pregnancy and lactation

Streptase is contra-indicated in pregnancy.

There is no evidence from the drug's safety in pregnancy nor is there any evidence from animal work that it is free from hazard. Bleeding and anaphylactic reactions might cause abortion and fetal death, especially when Streptase is given within the first 18 weeks of pregnancy. Use only when there is no safer alternative and when the disease (as, for example, in individual cases of massive pulmonary embolism) carries a high risk for the mother.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Early reactions: Fever and chills, headache, gastrointestinal symptoms and musculoskeletal pain may occur, but usually respond well to symptomatic therapy.

If hypotension occurs, it can usually be controlled by temporarily slowing the infusion rate. Tachycardia or bradycardia have been observed occasionally.

Patients may develop allergic-anaphylactic reactions (e.g. rash, flushing, dyspnoea). Allergic reactions can be largely avoided by giving the initial intravenous dose slowly. Corticosteroids can also be given prophylactically (e.g. 100-250 mg methylprednisolone 10 minutes before starting streptokinase treatment). If an allergic reaction occurs the infusion should be discontinued and the patient given intravenous corticosteroids together with adrenaline and an antihistamine. Once the symptoms have subsided, treatment can be continued with Streptase or urokinase.

Treatment of anaphylactic shock: Discontinue Streptase immediately. Adrenaline should be given immediately by slow intravenous injection. In addition, high doses of corticosteroids by slow intravenous injection may be given.

Streptokinase administration has been associated with low back pain. This may indicate an allergic response, and it may be appropriate to discontinue the infusion. In some cases, without other features of allergy, infusion has been continued with analgesic cover, without adverse consequence.

Haemorrhage: Minor bleeding may occur at infusion or puncture sites. Discontinuation of treatment is not necessary. In serious haemorrhagic complications, streptokinase therapy should be discontinued and a proteinase inhibitor, e.g. aprotinin, should be given in the following dosages:

Initially 500,000 KIU to one million KIU by slow intravenous injection or infusion (maximum rate 5 ml/min). If necessary this should be followed by 200,000 KIU four-hourly until the bleeding stops. In addition, combination with

synthetic antifibrinolytics is recommended. If necessary, clotting factors can be substituted.

Haemorrhage can occur in any tissue and organ in the body, and can present with symptoms affecting any body system, including the abdomen, cardiovascular system, joints and CNS. Cases of retinal haemorrhage have been reported rarely.

Haemorrhage should be considered as a potential cause of unusual symptoms occurring after administration.

Other reactions: In a few sporadic cases, neuroallergic symptoms (Guillain-Barré Syndrome, polyneuropathy) have been reported in temporal coincidence with Streptase administration.

Serum sickness has been reported but is rare.

Non-cardiogenic pulmonary oedema has been observed in a few cases, mainly after intracoronary thrombolytic therapy in patients with extensive myocardial infarction.

Transient increases in serum enzymes and a few cases of elevation of bilirubin levels have been reported. A few cases of cholesterol embolism have been described in temporal coincidence with thrombolytic therapy, particularly in patients undergoing angiography.

The risk of pulmonary embolism in patients with deep vein thrombosis is not greater during treatment with Streptokinase than during treatment with Heparin alone. If acute or recurrent pulmonary embolism occurs during the treatment, the course of Streptokinase should be continued as originally planned so as to lyse the emboli.

4.9 Overdose

Long term overdose of Streptokinase may induce the risk of Rethrombosis by prolonged decrease of plasminogen. (See also side-effects, haemorrhages).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Streptokinase is an enzyme obtained from β haemolytic streptococci of the lancefield group C. It is a potent activator of the fibrinolytic enzyme system in man and it acts directly by complexing with plasminogen to form an activator complex which then reacts with plasminogen to form plasmin.

5.2 Pharmacokinetic properties

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. The complex is biochemically inert and is cleared rapidly from the circulation. Once the antibody has been neutralised, the streptokinase activates plasminogen and the resulting complex acts on non complexed plasminogen to form plasmin. During these events the streptokinase is proteolytically modified into several lower molecular weight fragments.

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

5.3 Preclinical safety data

Extensive studies in different species of laboratory animals have shown that multiple human doses do not have an acute toxic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium glutamate
Polygeline
Human Albumin Solution 20% w/v which contains:
Human albumin
Acetyltryptophan
Sodium caprylate
Sodium chloride

6.2 Incompatibilities

Other drugs should not be added to the infusion solution.

6.3 Shelf Life

Powder for sterile concentrate:	3 years.
Concentrated solution:	24 hours*.
Solution for infusion:	24 hours*.

*The sum of the storage period for the sterile concentrate and the solution for infusion should be not more than 24 hours.

6.4 Special precautions for storage

Powder for sterile concentrate.

Do not store above +25°C.

Concentrated Solution

After being dissolved in 5ml saline (0.9%), the Streptase concentrated solution can be stored in a refrigerator at +2 to +8°C for 24 hours without loss of activity, only if prepared aseptically. However, if prepared non-aseptically, the concentrated solution should be used immediately.

Solution for infusion

After diluting the concentrated solution in 50-200ml infusion fluid, the Streptase infusion may be stored at +2°C to +8°C for up to 24 hours, including the period stored as the concentrated solution, i.e. the sum of the storage period for the concentrated solution and the infusion solution should be not more than 24 hours.

6.5 Nature and contents of container

1 x 5ml glass vial (Type I, Ph.Eur.), with chlorobutyl rubber stopper and aluminium/polypropylene cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Preparation of concentrated solution:

Streptase powder for sterile concentrate should be reconstituted by injecting 5mls reconstitution solution (preferably 0.9% saline) into the vial through the stopper and directing the diluent at the powder. This will cause the powder 'cake' to break-up into pieces. Vent the vial by loosening the syringe needle so that the remaining vacuum is abandoned. Foam which might have been formed will break down. Finally, by tilting and rolling the vial, the dissolution of the freeze-dried powder can be accelerated.

Streptase concentrated solution should not be injected directly but must be first diluted as a solution for infusion.

Preparation of solution for infusion:

The concentrated solution dissolves in 50-200ml 0.9% saline, 5% glucose, 5% fructose, Ringer-lactate solution or Haemaccel.

7 MARKETING AUTHORISATION HOLDER

Hoechst Marion Roussel Ireland Ltd
Cookstown
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 855/14/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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