Streptase®

Active ingredient: Stabilized pure streptokinase, derived from the culture filtrate of beta-haemolytic streptococci of Lancefield group C. It is presented as a white powder and contains stabilizers.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients

Streptase 1 500 000:
1 injection vial with 147 to 192 mg dried substance contains 1 500 000 IU streptokinase.

Streptase 750 000:
1 injection vial with 139 to 182 mg dried substance contains 750 000 IU streptokinase.

Other ingredients
Human albumin, Sodium-L-hydrogen glutamate monohydrate, Sodium dihydrogenphosphate dihydrate, Disodium hydrogenphosphate dihydrate.

PHARMACEUTICAL FORM AND PRESENTATIONS

Pharmaceutical form
Powder for intravenous or intraarterial administration after reconstitution with physiological saline.

Presentations
Streptase 1 500 000
1 vial of 1 500 000 IU streptokinase
Streptase 750 000
1 vial of 750 000 IU streptokinase

PHARMACOTHERAPEUTIC GROUP
Streptokinase (antithrombotic agents, enzymes).
ATC-code: B01A D01

THERAPEUTIC INDICATIONS

Streptase 750,000 IU: Acute myocardial infarction, deep vein thrombosis, pulmonary embolism, acute or subacute thrombosis of peripheral arteries and chronic occlusive arterial diseases, occlusion of central retinal artery or vein.

Streptase 1,500,000 IU:
Systemic administration: in deep vein thromboses, lung embolism, acute myocardial infarction for re-opening of coronary vessels. In acute and subacute thromboses of peripheral arteries and chronic occlusive arterial diseases, occlusion of central retinal artery or vein.

Local administration: in acute myocardial infarction for re-opening of coronary vessels, in acute, subacute and chronic thromboses as well as embolisms of peripheral arteries.

CONTRAINDICATIONS

Streptase must not be used in case of severe allergic reactions to the product.

Because of the increased risk of haemorrhage under thrombolytic therapy, Streptase 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 insultus, intracranial or intraspinal surgery
- intracranial neoplasm
- recent head trauma
- arteriovenous malformation or aneurysm
- known neoplasm with risk of haemorrhage
- acute pancreatitis
- uncontrollable hypertension with systolic values above 200 mmHg and/or diastolic values above 100 mmHg or hypertensive retinal changes grades III/IV
- recent implantation of a vessel prothesis
- simultaneous treatment with oral anticoagulants (drugs which inhibit the coagulation) (INR>1.3)
- severe liver or kidney damages
- endocarditis or pericarditis. Isolated cases of a pericarditis, misdiagnosed as acute myocardial infarction and treated with Streptase, have resulted in pericardial effusions including tamponade.
- known bleeding tendency
- recent major operations (6^{th} to 10^{th} postoperative day, depending on the severity of surgical intervention)
- invasive operations, e.g. recent organ biopsy, long-term closed-chest cardiac massage.

Local administration
Also in local administration a systemic effect is possible. Therefore, the contraindications mentioned above should also be considered for local administration.

Pregnancy and lactation
Due to the risk for the fetus, Streptase should only be given during pregnancy after careful benefit-risk consideration. In the first 18 weeks of pregnancy, the use of streptokinase must be restricted to vital indications only.

Information on the use of Streptase during breast-feeding is not available.

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 lumbar route (angiography of principal artery of the lumbar vertebrae section)
- recent trauma and cardiopulmonary resuscitation
- invasive operations, e.g. recent intubation
- puncture of non-compressible vessels, intramuscular injections
- recent delivery, abortion (including miscarriage)
- diseases of the urogenital tract with existing or potential sources of bleeding (implanted bladder catheter)
- known septic thrombotic disease
- severe atherosclerotic vessel degeneration, cerebrovascular diseases
- cavernous diseases (e.g. open tuberculosis)
- mitral valve defects or atrial fibrillation.

Local administration
A systemic effect is also possible during local administration. Therefore, the special warnings mentioned above should also be considered for local administration.

Antistreptokinase antibodies
Because of the increased likelihood of resistance due to antistreptokinase antibodies, re-treatment with Streptase 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, acute glomerulonephritis.

Infusion rate and corticosteroid prophylaxis
At the beginning of therapy, fall in blood pressure, increase in heart rate or decrease in heart rate (in individual cases reaching as far as shock) are commonly observed. Therefore, at the beginning of therapy the infusion should be performed slowly. Furthermore, corticosteroids can be administered prophylactically.

Pre-treatment with heparin or coumarin derivatives
If the patient is under active heparinization, it should be neutralized 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 acid and streptokinase on the life-expectancy of patients with suspected myocardial infarction has been observed. The administration of acetylsalicylic acid should commence prior to the streptokinase therapy and be continued for at least one month.

Arterial puncture
Should an arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. After the puncture, pressure should be applied for at least 30 minutes by a compression bandage, and the puncture site should be checked frequently for evidence of bleeding.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Simultaneous or previous treatment with anticoagulants or substances which inhibit the platelet formation or function (e.g. platelet aggregation inhibitors, dextrans) may increase the danger of haemorrhage.
Before starting long-term systemic lysis of deep vein thromboses and arterial occlusions with streptokinase, the effects of drugs which act upon platelet formation or function should be allowed to subside (see “Special warnings and precautions for use”).

Incompatibilities
Not known.
For further dilution of the reconstituted solution special infusion solutions are recommended (see also “Administration”).

DOSAGE AND ADMINISTRATION

Dosage

Note: When thrombolytic therapy is necessary or a high antibody concentration against streptokinase is present, or recent streptokinase therapy has been given (more than 5 days and less than one year previously), homologous fibrinolytics should be used (see also “Special warnings and precautions for use”).

Acute transmural myocardial infarction with persistent ST-segment elevation or recent left bundle-branch block:

Systemic administration
In short-term lysis for the treatment of acute myocardial infarction 1.5 Mio IU Streptase are given within 60 min.

Local administration
In acute myocardial infarction patients are given an intracoronary bolus of 20 000 IU Streptase on average and a maintenance dose of 2000 IU to 4000 IU per min over 30 to 90 min.

Acute, subacute and chronic thromboses/embolisms of peripheral venous and arterial vessels and chronic occlusive arterial diseases:

Systemic administration
In short-term thrombolysis, adults with peripheral venous and arterial vessel occlusions/ embolism, receive an initial dose of 250 000 IU Streptase within 30 min, followed by a maintenance dose of 1.5 Mio IU per hour over a maximum of six hours. The six-hour Streptase infusion can be repeated on the following day, depending on the therapeutic success of lysis. However, repetition of treatment must on no account be conducted later than 5 days after the first course.

As an alternative to short-term lysis, a long-term lysis for the treatment of peripheral occlusions may be considered. An initial dose of 250 000 IU Streptase is given within 30 min, followed by a maintenance dose of 100 000 IU per hour. The duration of therapy depends on the extension and localisation of the vessel occlusion. In peripheral vessel occlusion the maximum duration is 5 days.

Local administration
Patients with acute, subacute and chronic peripheral thromboses and embolisms receive 1000 IU to 2000 IU Streptase in intervals of 3 to 5 min. The duration of administration depends on the length and localisation of the vessel occlusion and amounts up to 3 hours at a total dose of max. 120 000 IU Streptase.
A percutaneous transluminal angioplasty can be performed simultaneously, if necessary.

Occlusions of central retinal artery or vein:

Systemic administration
In case of thromboses of the central retinal vessels, lysis of arterial occlusions should be limited to max. 24 hours and in venous occlusions to max. 72 hours. If continuation of thrombolysis is indicated due to extensive thrombotic occlusions, therapy should be interrupted for one day, followed by administration of a homologous fibrinolytic.

Dosage for neonates, infants and children:
Sufficient experience with Streptase therapy in children is not yet available. The benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

Control of therapy

Systemic administration
In case of short-term lysis over six hours heparin should be administered during or following Streptase infusion when the thrombin time (TT) or partial thromboplastin time (aPTT) have reached less than twice or 1.5 times the normal control value, respectively. The TT and aPTT should be prolonged to 2 to 4 fold and 1.5 to 2.5 fold the normal value, respectively, in order to ensure sufficient protection against rethrombosis.
If the Streptase infusion is not repeated the heparin therapy is instituted simultaneously with the administration of oral anticoagulants (see *Follow-up treatment*).

The long-term lysis is controlled with the thrombin time (TT*)*. A 2 to 4 fold prolongation of the TT which is considered as a sufficient anticoagulant protection has to be aimed at. Therefore, a simultaneous administration of heparin may become necessary from the 16th hour of treatment. If the TT after the 16th hour is still prolonged to more than 4 fold the normal control value, the maintenance dose of Streptase has to be doubled for several hours until the TT recedes.

Local administration
As is usual with angiographies (x-ray of the vessels with the help of contrast media), heparin is administered, if necessary, prior to the angiography as a safeguard against catheter-induced thromboses. The success of therapy can be determined by the angiography. With a sufficient blood flow of more than 15 minutes the therapy can be considered successful and then terminated.

Follow-up treatment
After every course of streptokinase therapy a follow-up treatment with anticoagulants or platelet aggregation inhibitors can be instituted as a prevention of rethromboses. With heparin therapy, in particular, an increased risk of haemorrhage must be considered. The heparin therapy is controlled individually with the TT or aPTT. A 2 to 4 fold prolongation of the TT and 1.5 to 2.5 fold prolongation of the aPTT is aimed for. For long term prophylaxis oral anticoagulants, such as coumarin derivatives or platelet aggregation inhibitors can be applied.

Administration
Streptase is administered intravenously or intraarterially. The duration of therapy depends on the nature and extension of the vessel occlusion and differs according to the indication (see “Dosage”).

Streptase is presented as a white lyophilisate. Upon reconstitution with physiological saline, a colourless to yellowish, clear solution is obtained.

To ensure that the contents of the vial are rapidly and completely reconstituted, 5 ml of physiological saline should be injected into the Streptase vacuum vial, and the residual vacuum abolished by briefly loosening the needle from the syringe.

For administration with an infusion pump, physiological saline, Ringer-lactate solution, 5% glucose or laevulose solution can be used as diluent. For higher dilutions, especially when good stability is required over longer periods, polygeline can be used as diluent.

UNDESIRABLE EFFECTS

If you experience reactions, especially those which are not mentioned in this package insert, please inform your doctor or pharmacist.

The following adverse reactions are based on experience from clinical trials and on postmarketing experience. The following standard categories of frequency are used:

Very common	>	*1/10*
Common	>	1/100 and < 1/10
Uncommon	>	1/1,000 and < 1/100
Rare	>	1/10,000 and < 1/1,000
Very rare	<	1/10,000 (including reported single cases)

Blood disorders
- *Common*: Haemorrhages at the injection site and ecchymoses. Gastrointestinal or urogenital bleedings, epistaxis.
- *Uncommon*: Cerebral 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.
- *Very rare*: Haemorrhages into the pericardium including myocardial rupture during thrombolytic treatment of acute myocardial infarction.

  In severe haemorrhagic complications the Streptase therapy is discontinued and a proteinase inhibitor, e.g. aprotinin, administered in the following dosage: Initially 500 000 KIU , if necessary up to 1 million KIU, followed by 50 000 KIU per hour by intravenous drip until the bleeding stops. In addition, combination with synthetic antifibrinolytics is recommended. If necessary, coagulation factors can be administered. Additional administration of synthetic antifibrinolytics was reported to be efficient in single cases of bleeding episodes.

Immune system disorders
- *Very common*: Development of antistreptokinase antibodies (see also “Special warnings and special precautions for use”).
- *Common*: Allergic-anaphylactic reactions with rash, flushing, itching, urticaria, angioneurotic edema, dyspnoea, bronchospasm or fall in blood pressure.
- *Very rare*: Delayed allergic reactions, such as serum sickness, arthritis, vasculitis, nephritis and neuroallergic symptoms, polyneuropathy,(e.g. Guillain Barré syndrome), severe allergic reactions up to shock including respiratory arrest.

Mild or moderate allergic reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. If a severe allergic/anaphylactic reaction occurs the administration of Streptase has to be discontinued immediately and an appropriate treatment should be initiated. The current medical standards for shock treatment should be observed. Lysis therapy should be continued with homologous fibrinolytics.

Nervous system disorders
- *Rare*: Neurologic symptoms (e.g. dizziness, confusion, paralysis, hemiparesis, restlessness or convulsions in the context of cerebral haemorrhages or cardiovascular disorders with hypoperfusion of the brain.

Cardiac complication and vascular disorders
- *Common*: At the beginning of therapy fall in blood pressure, tachycardia or bradycardia (see also “Special warnings and special precautions for use”, subheading “Infusion rate and corticosteroid prophylaxis”).
- *Very rare*: Crystal cholesterol embolism.

In the setting of fibrinolytic therapy with Streptase in patients with myocardial infarction the following events have been reported as complications of myocardial infarction and/or symptoms of reperfusion:
- *Very common*: Fall in blood pressure, heart rate and rhythm disorders, angina pectoris
- *Common*: Recurrent ischaemia (depletion of blood), heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema.

These cardiovascular complications can be life-threatening and may lead to death.

During local lysis of peripheral arteries, distal embolization cannot be excluded.

Respiratory disorders
- *Very rare*: Non-cardiogenic pulmonary edema after intracoronary thrombolytic therapy in patients with extensive myocardial infarction.

Gastrointestinal disorders
- *Common*: Nausea, diarrhoea, epigastric pain and vomiting.

General disorders
- *Common*: Headache and back pain, muscle pain, chills and/or rise in temperature as well as faintness/ weariness.

Investigations
- *Common*: Transient elevations of serum transaminases (liver function parameters) as well as of bilirubin.

STORAGE AND STABILITY

Streptase is to be stored at +2 to +25 °C.

Once reconstituted with physiological saline, the physico-chemical stability has been demonstrated for 24 hours at +2 to +8 °C. From a microbiological point of view and as Streptase 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 °C.

Streptase must not be used after the expiry date given on the pack and container.

Keep out of the reach of children!

Manufacturer:
CSL Behring GmbH, Germany
Emil-von-Behring-Str.76
D-35041 Marburg
Germany
Registration holder: Genmedix, 12 Beit Harishonim St. Emek-Hefer 38777

The format of this leaflet has been determined by the Ministry of Health and its content has been examined and approved in November 2012.

SH Z550051009999B/STR OCT14