SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Streptokinase Karma 750 000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Streptokinase Karma 250 000 and 750 000 are presented as a powder for solution in vials containing 250 000 and 750 000 International Units (IU) of purified streptokinase as the active ingredient. For a full list of excipients, see section 6.1.

Highly purified streptokinase is extracted from the culture filtrate of certain strains of the streptococcus group C. It is presented as a white to slightly yellow powder and contains stabilisers.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to slightly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Streptokinase Karma is indicated in adults.

Streptokinase Karma is a fibrinolytic agent which may be used for the intravascular dissolution of thrombi and emboli in:

- acute massive pulmonary embolism
- acute, sub-acute or chronic (not older than 6 weeks) occlusion of peripheral arteries
- extensive deep vein thrombosis
- central retinal venous or arterial thrombosis (arterial occlusions not older than 8 hours, venous occlusions not older than 10 days).

Note: No statement on therapy outcome can be made for administration beyond the time windows indicated above.

4.2 Posology and method of administration

Posology

Adults

Deep vein thrombosis

An initial dose of 250 000 IU streptokinase should be infused into a peripheral vein over 30 minutes. A maintenance infusion of 100 000 IU/hour for 72 hours should follow.

Pulmonary embolism

Infuse 1 500 000 IU streptokinase into a peripheral vein preferably over a short time of 1-2 hours.

As an alternative, an initial dose of 250 000 IU streptokinase should be infused into a peripheral vein over 30 minutes. A maintenance infusion of 100 000 IU/hour for 24 hours should follow.

Occlusive peripheral arterial diseases

Administer streptokinase with a local intra-arterial catheter-directed infusion using one of the following regimes:

- Gradual infusion: 1000 to 2500 IU streptokinase at an interval of 3 to 5 minutes for a maximum of 10 hours and a total maximum dose of 250 000 IU

- Prolonged continuous low-dose infusion (using an infusion pump): 5000 to 10,000 IU streptokinase per hour for up to 5 days maximum.

A percutaneous transluminal angioplasty can be performed simultaneously, if necessary.

As an alternative for difficult arterial access or multiple occlusions, an initial dose of 250 000 IU streptokinase should be infused over 30 minutes. A maintenance infusion of 100 000 IU/hour for a maximum of 5 days should follow.

Central retinal vessel occlusion

An initial dose of 250 000 IU streptokinase should be infused into a peripheral vein over 30 minutes. A maintenance infusion of 100 000 IU/hour for 12 hours should follow.

Paediatric population

The safety and efficacy of Streptokinase Karma have not been sufficiently established in children. Due to low levels of plasminogen in newborns and in children with acquired plasminogen deficiency and due to the potential of streptokinase for allergic/anaphylactic reactions, it is not recommended in neonates, infants and children.

Control of Therapy

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 the thrombolytic therapy is started.

In patients previously treated with coumarin derivatives, the INR (international normalised ratio) should be below 1.3 before starting therapy with streptokinase.

Method of Administration

The administration of streptokinase may be by systemic intravenous infusion or by local intra-arterial catheter-directed infusion.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Upon reconstitution with physiological saline a clear solution, colourless to yellowish, is obtained.

Note: When thrombolytic therapy is necessary and a high antibody concentration against streptokinase is present or when recent streptokinase therapy has been given

(more than 5 days and less than one year previously), homologous fibrinolytics should be used (see sections 4.4 and 4.8).

Systemic Administration

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

A 2 to 4 fold prolongation of the TT should be aimed for and is considered a sufficient anticoagulation protection. If the thrombin time or any other parameter of lysis after 4 hours of therapy is less than approximately 1.5 times the normal control value, discontinue Streptokinase Karma as excessive resistance to streptokinase is present.

Local administration

As is usual with angiographies, 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 stopped.

Follow-up treatment

After every course of streptokinase therapy, follow-up treatment with anticoagulants or platelet aggregation inhibitors can be instituted as prevention of rethromboses. With heparin therapy, in particularly, an increased risk of haemorrhage must be considered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications to treatment with Streptokinase Karma, because of the increased risk of haemorrhage under thrombolytic therapy, include:

- existing or recent internal haemorrhage
- all forms of reduced blood coagulability, in particular spontaneous fibrinolysis and extensive clotting disorders
- recent cerebrovascular accident, 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 over 200 mm Hg and/or diastolic values over 100 mm Hg or hypertensive retinal changes Grades III/IV
- recent implantation of a vessel prosthesis
- simultaneous or recent treatment with oral anticoagulants (INR >1.3)
- severe liver or kidney damage
- endocarditis or pericarditis. Isolated cases of pericarditis, misdiagnosed as acute myocardial infarction and treated with streptokinase, have resulted in pericardial effusions including tamponade
- known haemorrhagic diathesis
- recent major operations (6th to 10th post-operative day, depending on the extent of the procedure)
- invasive operations, e.g. recent organ biopsy, long-term (traumatic) closed chest cardiac massage

4.4 Special warnings and precautions for use

The following conditions would normally be considered contraindications to streptokinase therapy, but in certain situations the benefits could outweigh the potential risks:

- recent severe gastrointestinal bleeding, e.g. active peptic ulcer
- risk of severe local haemorrhage, e.g. in case of translumbar aortography
- recent trauma and cardiopulmonary resuscitation
- invasive operations, e.g. recent intubation
- puncture of non-compressible vessels, intramuscular injections, large arteries
- recent abortion or delivery
- pregnancy (see section 4.6)
- diseases of the urogenital tract with existing or potential sources of bleeding (implanted bladder catheter)
- known septic thrombotic disease
- severe arteriosclerotic vessel degeneration, cerebrovascular diseases

- cavernous pulmonary diseases, e.g. open tuberculosis or severe bronchitis
- mitral valve defects or atrial fibrilation
- diabetic retinopathy increase risk of local bleeding

Antistreptokinase

Repeat treatment with streptokinase administered more than 5 days and less than 12 months after initial treatment may not be effective. This is because of the increased likelihood of resistance due to antistreptokinase antibodies.

Also, 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 going as far a shock) are 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 administering 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.

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. The puncture site should be checked frequently for evidence of bleeding.

Streptokinase is not indicated for restoration of patency of intravenous catheters.

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, e.g. heparin or drugs which inhibit platelet formation or function, e.g. platelet aggregation inhibitors, dextrans.

The effects of drugs which act upon platelet formation or function should be allowed to subside before starting long-term lysis of deep vein thromboses and arterial occlusions with streptokinase (see section 4.2).

4.6 Fertility, Pregnancy and lactation

Streptokinase Karma is contraindicated in pregnancy. There is no evidence of the drug's safety in pregnancy, nor is there evidence from animal work that it is free from hazard. Bleeding and anaphylactic reactions might cause abortion and foetal death, especially when streptokinase is given within the first 18 weeks of pregnancy. Use only when there is no safer alternative.

It is unknown whether streptokinase is excreted in human milk. Breast milk should be discarded during the first 24 hours following thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following adverse reactions are based on clinical trial and post-marketing experience. The following standard categories are used:

Very common	more than1/10
Common	more than 1/100; less than 1/10
Uncommon	more than 1/1000; less than 1/100
Rare	more than 1/10,000; less than 1/1000
Very Rare	less than1/10,000 (including isolated cases)

Blood and lymphatic system disorders
Common: haemorrhage at the injection site, ecchymoses, gastrointestinal bleeding, genitourinary bleeding, epistaxis
Uncommon: cerebral haemorrhages with their complications and possible fatal outcome, retinal haemorrhages, severe haemorrhages (also with fatal outcome), liver haemorrhages, retroperitoneal bleeding, bleeding into joints, splenic rupture. Blood transfusions are rarely required.
Very rare: haemorrhage into the pericardium including myocardial rupture during thrombolytic treatment of acute myocardial infarction

In serious haemorrhagic complications, streptokinase therapy should be discontinued and a proteinase inhibitor, e.g., aprotinin, should be given as follows. Initially 500 000 KIU (Kallikrein Inactivator Unit) up to one million KIU by slow intravenous injection or infusion. If necessary this should be followed by 200,000 KIU every four hours by intravenous drip until the bleeding stops. In addition, combination with synthetic antifibrinolytics is recommended. If necessary, clotting factors can be substituted. Additional administration of synthetic antifibrinolytics has been reported to be efficient in single cases of bleeding episodes.

Immune system disorders
Very Common: development of antistreptokinase antibodies (see also 4.4)
Common: allergic anaphylactic reactions, e.g. rash, flushing, itching, urticaria, angioneurotic oedema, dyspnoea, bronchospasm, hypotension
Very Rare: delayed allergic reactions, e.g. serum sickness, arthritis, vasculitis, nephritis, neuroallergic symptoms (polyneuropathy, e.g. Guillain Barré syndrome), severe allergic reactions up to shock including respiratory arrest.

Moderate or mild allergic reactions can be managed with concomitant antihistamine and/or corticosteroid therapy. If a severe allergic reaction occurs the infusion of streptokinase should be discontinued immediately and the patient given the appropriate treatment. The current medical standards for shock treatment should be observed. Lysis therapy should be continued with homologous fibrinolytics, such as Urokinase or tPA
Nervous system disorders
Rare: neurologic symptoms (e.g. dizziness, confusion, paralysis, hemiparesis, agitation, convulsion) in the context of cerebral haemorrhages or cardiovascular disorders with hypoperfusion of the brain

Eye disorders
Very rare: iritis/uveitis/iridocyclitis

Cardiac and vascular disorders
Common: at the start of therapy, hypotension, tachycardia, bradycardia
Very rare: crystal cholesterol embolism

During fibrinolytic therapy with streptokinase in patients with myocardial infarction, the following events have been reported as complications of myocardial infarction and/or symptoms of reperfusion:
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 peripheral embolism

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 oedema after intracoronary thrombolytic therapy in patients with extensive myocardial infarction

Gastrointestinal disorders
Common: nausea, diarrhoea, epigastric pain, vomiting

General disorders and administration site conditions
Common: headache, back pain, musculoskeletal pain, chills, fever, asthenia, malaise

Testing
Common: Transient elevations of serum transaminases and bilirubin

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: *www.mhra.gov.uk/yellowcard*.

4.9 Overdose

Long-term overdosage of streptokinase may induce the risk of rethrombosis by prolonged decrease of plasminogen. See also section 4.8 and 5.1.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Streptokinase (antithrombotic agents, enzymes)
ATC code: B01A D01

Streptokinase Karma is a highly purified streptokinase derived from β haemolytic streptococci of Lancefield 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 titre, 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 the plasminogen as described above.

5.2 Pharmacokinetic properties

The elimination kinetics of streptokinase follows a biphasic course. A small proportion of the dose is bound to anti-streptokinase antibodies and metabolised with

a half-life of 18 minutes while most of it forms a streptokinase-plaminogen activator complex and is biotransformed with a half-life of about 80 minutes.

Peak fibrinolytic activity is found in the blood about 20 minutes after dosing.

Like other proteins, streptokinase is metabolised proteolytically in the liver and eliminated via the kidneys. Animal data suggest that streptokinase may also be excreted unchanged in the bile.

5.3 Preclinical safety data

In an Ames Test on Streptokinase Karma, no evidence of mutagenic potential was found. No other preclinical safety studies have been performed on Streptokinase Karma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin, Aminoacetic acid (glycine), Mannitol

6.2 Incompatibilities

No incompatibilities have been reported when Streptokinase Karma is used as recommended. This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The shelf-life of unopened vials of Streptokinase Karma 250 000 and 750 000 is 3 years.

6.4 Special precautions for storage

Do not store above +25°C and do not freeze.

Do not store the reconstituted solution for more than 24 hours in a refrigerator at +2°C to +8°C.

6.5 Nature and contents of container

Streptokinase Karma 250 000 and 750 000 is supplied in 10 ml glass vials with rubber closures and aluminium seal with plastic flip-top caps.

Streptokinase Karma 250 000 and 750 000 is available in packages containing one vial.

6.6 Special precautions for disposal

The contents should be dissolved in 4-5 ml of physiological saline or water for injection. The solution should be swirled gently to facilitate quick reconstitution, but care should be taken to avoid foaming.

Physiological saline, 5% glucose solution, 5% fructose solution, or Ringer-lactate solution can be used as a diluent for administration with an infusion pump.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Karma Pharmatech GmbH
Emil-von-Behring-Str. 76
35041
Marburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 49427/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/1998 / 15/05/2009

10 DATE OF REVISION OF THE TEXT

01/07/2024