SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Streptokinase Karma 750 000

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Streptokinase Karma is presented as a freeze-dried powder in vials.
Each vial of Streptokinase Karma 750 000 contains 750 000 International Units (IU) of purified streptokinase (257-314 mg freeze-dried powder).

3 PHARMACEUTICAL FORM

Freeze-dried powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- pulmonary embolism
- acute or sub-acute occlusion of peripheral arteries
- extensive deep vein thrombosis
- central retinal venous or arterial thrombosis.

4.2 Posology and method of administration

Streptokinase Karma should be given by intravenous infusion in 50-200 ml of physiological saline, 5% glucose or Ringer-lactate solution. An initial loading dose to neutralise circulating streptococcal antibodies is followed by a maintenance does to continue fibrinolysis.

Loading dose
A dose of 250 000 IU Streptokinase Karma infused into a peripheral vein over 30 minutes has been found appropriate in over 90% of patients.
A maintenance infusion of 100 000 IU/hour is given after the loading dose. Administer the maintenance dose 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 vessel thrombosis.

Control of Therapy
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.

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 IU/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 the 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 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 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 Treatment
At the end of Streptokinase Karma 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 3-4 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

Contraindications to treatment with Streptokinase Karma 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 contraindications 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 8th 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 (If thrombolytic therapy is necessary when a high antibody concentration against streptokinase is present or when the patient has recently been treated with streptokinase, urokinase can be used instead.)
- subacute bacterial endocarditis
- severe hypertension with systolic values over 200mm Hg or diastolic values over 100 mm Hg 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
- septic thrombotic disease
- pregnancy (see section 4.6)
- aortic dissection
- pericarditis
- aneurism.

4.4 Special warnings and precautions for use

Special Warnings

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. 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 Streptokinase Karma. See also section 4.2 “Posology and method of administration (Patient Monitoring)”.

Chest compression warning.

If the patient has been receiving heparin, its effects can be neutralised by giving protamine sulphate.

In patients previously treated with coumarin derivatives, the INR (international normalised ratio) should be below 1.7 before starting therapy with streptokinase.

Precaution for Use

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

Caution is necessary in patients with diabetic retinopathy as there may be an increased risk of local bleeding.

In the following conditions, streptokinase is unlikely to be effective:

- deep vein thrombosis more than 14 days old,
- occlusion of the central retinal artery more than 6-8 hours old, and
- thrombosis of the central retinal vein more than 10 days old.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants and drugs which affect platelet formation and function (e.g., heparins, coumarin, derivatives, dipyridaole, dextrans) have an intrinsic potential to interact with streptokinase. To avoid an elevated bleeding risk, it is therefore essential that the activity of such drugs be neutralised or allowed to subside prior to streptokinase therapy. See also section 4.2 “Posology and method of administration (Patient Monitoring)” and section 4.4.1 “Special Warnings”.

4.6 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 anaphlylactic reactions might cause abortion and foetal death, especially when Streptokinase Karma 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 degree of risk for the mother.

It has not been established whether streptokinase is safe to use during breast-feeding.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Early Reactions

Fever and chills, headache, gastrointestinal symptoms, nausea, vomiting, convulsions, and back or 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 occasionally been observed.

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Patients may develop allergic reactions (e.g., rash, flushing, dyspnoea). Allergic reactions can largely be 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 Streptokinase Karma or urokinase. 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 any other signs of allergy, infusion has been continued with analgesic cover, without adverse consequences.

Anaphylactic reactions have rarely been observed. If an anaphylactic reaction occurs, discontinue the infusion immediately and immediately give adrenaline by slow intravenous injection. In addition, high doses of corticosteroids by slow intravenous injection may be given.

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 as follows.
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 be present with symptoms affecting any body system, including the abdomen, cardiovascular system, joints and CNS. 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 administration of streptokinase.
Uveitis has been reported in temporal association with streptokinase administration.
Serum sickness has been reported but is rare.
Reperfusions arrhythmias, recurrent ischaemia, and angina have been reported.
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.
Non-cardiogenic pulmonary oedema has been observed in a few cases.
Transient increase in serum enzymes and a few cases of elevation of bilirubin levels have been reported. Jaundice may occur as consequence of bilirubin increase. A few cases of cholesterol embolism have been described in temporal coincidence with thrombolytic therapy particularly in patients undergoing angiography.

4.9 Overdose

Long-term overdosage of streptokinase may induce the risk of rethrombosis by prolonged decrease of plasminogen. See also section 4.8 “Undesirable effects (Haemorrhage)”.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Streptokinase Karma activates the intrinsic fibrinolytic system by the formation of a linkage compound between streptokinase and the proactivator plasminogen molecule. This complex possesses activator properties and brings about the conversion of plasminogen into the fibrinolytic enzyme plasmin. Plasminogen absorbed on to the fibrin clot is also activated, therefore lysis can take place internally as well as externally.

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, whilst most of it forms the streptokinase-plasminogen activator complex and is biotransformed with a half-life of about 80 minutes.
Like other proteins, streptokinase is metabolised proteolytically in the liver and eliminated via the kidneys.

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. Plasma expanders such as dextrans interfere with coagulation and are therefore not suitable for use as vehicles with streptokinase. See also section 4.4.1 “Special warnings” and section 6.6 “Instructions for use/handling”.

6.3 Shelf-life

The shelf-life of unopened vials of Streptokinase Karma to be stored below 25°C is 24 months. Do not freeze the product.

6.4 Special precautions for storage

The freeze-dried powder should be stored below 25°C and should not be frozen.
The reconstituted solution should not be stored for more than 12 hours in a refrigerator at 2°C to 8°C.

6.5 Nature and contents of container

Streptokinase Karma is supplied in 10 ml glass vials with rubber closures and aluminium flip-top caps.
Streptokinase Karma 750 000 is available is packages containing one or five vials.

6.6 Instructions for use, handling and 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 reconstitution, but care should be taken to avoid foaming. Suitable vehicles for streptokinase infusions are physiological saline, 5% glucose and Ringer-lactate solution.

ADMINISTRATIVE DATA

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 40718/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10 DATE OF REVISION OF THE TEXT

February 2019