PRODUCT MONOGRAPH

STREPTASE®
(**Streptokinase Injection**)

250,000 IU; 750,000 IU; 1,500,000 IU

Fibrinolytic Agent

CSL Behring Canada, Inc.
55 Metcalfe Street, Suite 1460
Ottawa, Ontario
KIP 6L5

Date of Approval:
Date of Revision:　February 23, 2007

Submission Control No:　112482

PRODUCT MONOGRAPH

NAME OF DRUG

STREPTASE®
(Streptokinase Injection)

250,000 IU; 750,000 IU; 1,500,000 IU

THERAPEUTIC CLASSIFICATION

Fibrinolytic Agent

ACTION AND CLINICAL PHARMACOLOGY

STREPTASE® (streptokinase injection) acts with plasminogen (or plasmin) to produce an "activator complex" that converts residual plasminogen into the proteolytic enzyme, plasmin. Plasmin is capable of hydrolyzing fibrin into polypeptides; it also hydrolyzes fibrinogen and other plasma proteins. Since plasminogen is present in the thrombus/embolus, activation by STREPTASE® occurs within the thrombus/embolus as well as on its surface.

The activity of streptokinase is expressed in International Units (IU) and is a measure of its ability to cause lysis of a fibrin clot via the plasmin system *in vitro*. The effect on coagulation after intravenous administration may persist for 12 to 24 hours after discontinuation due to a decrease in plasma levels of fibrinogen and an increase in the amount of circulating fibrin(ogen) degradation products (FDP). Studies with radioactive streptokinase indicate two disappearance rates: a "fast" half-life of approximately 18 minutes due to the action of antibodies, and a "slow" half-life, operative in the absence of antibodies, of approximately 83 minutes. Effective blood level and disappearance rate are dependent upon availability of substrates and, thus, are only relative indices of the pharmacologic effects of the drug. The efficacy of STREPTASE® in the lysis of venous thrombi and massive pulmonary emboli has been established in clinical studies by angiographic evaluations, before and after treatment.

Two large, randomized, multicentre, placebo-controlled studies involving almost 30,000 patients have demonstrated that a 60-minute intravenous infusion of 1,500,000 IU of STREPTASE® significantly reduces mortality rates following a myocardial infarction. Concomitant oral administration of low-dose acetylsalicylic acid (ASA) (160 mg/day) over a period of one month was shown to significantly enhance this beneficial effect.

INDICATIONS AND CLINICAL USE

Acute Myocardial Infarction

STREPTASE® (streptokinase injection) is indicated for use in the management of suspected acute myocardial infarction, for the lysis of acute thrombi obstructing coronary arteries associated with evolving transmural myocardial infarction, for the improvement of ventricular function, and for the reduction of infarct size and mortality associated with acute myocardial infarction, when administered by the intravenous or intracoronary route, as well as for the reduction of congestive heart failure associated with AMI when administered by the intravenous route. In the high risk group with anterior myocardial infarction, one year mortality was significantly reduced in those patients who reperfused in response to streptokinase.

Thrombolysis following intravenous streptokinase is usually achieved within less than one hour. Early administration is correlated with greater clinical benefit.

Pulmonary Embolism

STREPTASE® is indicated in adults for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels. It is also indicated for embolization accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, preferably pulmonary arteriography via an upper extremity vein, or non-invasive procedures such as lung scanning.

Deep Vein Thrombosis

STREPTASE® is indicated for lysis of acute, extensive thrombi of the deep veins in adults such as those involving the popliteal and more proximal vessels. Diagnosis should be confirmed by ascending venography or other equally objective methods.

Studies have demonstrated a better salvage of valvular function and prevention of postphlebitic syndrome by the combined usage of STREPTASE® and heparin than by heparin alone.

Arterial Thrombosis and Embolism

STREPTASE® is indicated for the lysis of acute arterial thrombi and for the lysis of arterial emboli. However, the use of STREPTASE® in arterial emboli originating from the left side of the heart (e.g., in mitral stenosis accompanied by atrial fibrillation) should be avoided due to the danger of new embolic phenomena including those to cerebral vessels.

Arteriovenous Cannula Occlusion

STREPTASE® is indicated for clearing of totally or partially occluded arteriovenous cannulae as an alternative to surgical intervention when acceptable flow cannot otherwise be achieved.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, STREPTASE® (streptokinase injection) is contraindicated in the following conditions:

- Active or recent internal bleeding

- Recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)

- Intracranial neoplasm

- Uncontrollable hypertension with systolic values above 200 mm Hg and/or diastolic values above 100 mm Hg, or hypertensive retinal changes Grades III/IV

- All forms of reduced blood coagulability in particular spontaneous fibrinolysis and extensive clotting disorders

- Recent head trauma

- Known neoplasm with risk of hemorrhage

- Acute pancreatitis

STREPTASE® should not be administered to patients having experienced severe allergic reaction to the product.

WARNINGS

Bleeding

The aim of STREPTASE® (streptokinase injection) therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example at sites of needle punctures, are also lyzed and bleeding from such sites may occur.

Following intravenous high-dose brief-duration STREPTASE® therapy (1,500,000 IU over 60 minutes), in acute myocardial infarction, severe bleeding complications requiring transfusion are extremely rare (0.3-0.5%), and combined therapy with low-dose ASA (160 mg/day over a period of one month) does not appear to increase the risk of major bleeding. The addition of ASA to STREPTASE® may cause a slight increase in the risk of minor bleeding (3.1% without ASA vs 3.9% with ASA).

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with STREPTASE®. Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. When internal bleeding occurs it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

In the following conditions, the risks of therapy may be increased and should be weighed against the anticipated benefits:

- Recent (within 10 days) major surgery

- Recent delivery, abortion

- Recent organ biopsy, previous puncture of non-compressible vessels, intramuscular injections or intubation

- Recent (within 10 days) serious gastrointestinal bleeding

- Recent (within 10 days) trauma including cardiopulmonary resuscitation

- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation

- Subacute bacterial endocarditis or pericarditis; isolated cases of a pericarditis, misdiagnosed as acute myocardial infarction and treated with Streptase®, have resulted in pericardial effusions including tamponade

- Hemostatic defects including those secondary to severe hepatic or renal disease

- Pregnancy

- Cerebrovascular disease

- Pulmonary diseases with cavitation (e.g., open tuberculosis) or severe bronchitis

- Severe diabetes mellitus

- Diabetic hemorrhagic retinopathy

- Diseases of the urogenital tract with potential sources of bleeding

- Septic thrombophlebitis or occluded AV cannula at seriously infected site

- Suspicion of severe artherosclerotic degeneration

- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of STREPTASE® should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Arrhythmias

Rapid lysis of coronary thrombi may cause reperfusion atrial or ventricular dysrhythmia requiring immediate treatment. Careful monitoring for arrhythmia should be maintained during and immediately following administration of STREPTASE®.

Hypotension

Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis has been observed during intravenous STREPTASE® infusion in 1 to 10% of patients. Patients should be monitored closely and should symptomatic or alarming hypotension occur, appropriate treatment should be administered. This treatment may include a decrease in the intravenous STREPTASE® infusion rate. Smaller hypotensive effects are common and have not required treatment.

PRECAUTIONS

General

STREPTASE® (streptokinase injection) should be used in hospitals where the recommended diagnostic and monitoring techniques are available.

Non-cardiogenic pulmonary edema has been reported rarely in patients treated with streptokinase. The risk of this appears greatest in patients who have large myocardial infarctions and are undergoing thrombolytic therapy by the intracoronary route.

Rarely, polyneuropathy has been temporally related to the use of streptokinase.

Should pulmonary embolism or recurrent pulmonary embolism occur during streptokinase therapy, the originally planned course of treatment should be completed in an attempt to lyze these emboli. While pulmonary embolism may occasionally occur during STREPTASE® treatment, the incidence is no greater than when patients are treated with heparin alone.

Repeated administration

Because of the increased likelihood of resistance due to antistreptokinase antibodies, STREPTASE® may not be effective if administered more than 5 days after prior to streptokinase administration or streptokinase-containing products, particularly between 5 days and 12 months.

It is not known whether persisting high *in vitro* neutralization titres affect the efficacy and safety of repeat administration of streptokinase or steptokinase-containing compounds.

Likewise, the effect may be reduced in patients with recent streptococcal infections such as streptococcal pharyngitis, acute rheumatic fever, acute glomerulonephritis secondary to a streptococcal infection.

Use in Pregnancy

Experience in pregnant women has not shown that STREPTASE® increases the risk of fetal abnormalities if administered during pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, STREPTASE® should be used during pregnancy only if clearly needed.

Thrombolytic therapy should be avoided within the first 18 weeks of the pregnancy because of the risk of placental separation.

Use in Children

Safety and effectiveness of STREPTASE® in children have not been established.

Nursing Mothers

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 a woman who is to receive STREPTASE®.

Drug Interactions

The potential for an additive hypotensive effect should be borne in mind when STREPTASE® therapy is combined with antihypertensive agents, such as **ß**-blockers and glyceryl trinitrate.

Until information regarding the interaction between STREPTASE® and tissue plasminogen activator (tPA) is available, special care should be taken if such a combination is considered.

There is an increased risk of hemorrhage in:

- Patients previously receiving heparin or coumarin derivatives. The effect of heparin can, however, be rapidly neutralized by administering protamine sulphate. In the case of prior treatment with coumarin derivatives, the Quick value must be more than 50% before the beginning of lysis.

- Patients receiving simultaneous treatment with platelet-aggregation inhibitors, e.g., ASA (see below also), phenylbutazone, dipyridamole and non-steroidal anti-inflammatory drugs (NSAIDS).

- Patients receiving simultaneous or previous treatment with dextrans.

Combination of STREPTASE® with ASA for Treatment of Myocardial Infarction

In the treatment of acute myocardial infarction with intravenous STREPTASE® (1,500,000 IU over 1 hour) combined with enteric-coated ASA (160 mg/day for one month), it was shown that the combined treatment results in a further reduction in mortality rate, as well as a decreased risk of reinfarction and stroke in comparison to treatment with each of the drugs alone. The addition of ASA to STREPTASE® may cause a slight increase in the risk of minor bleeding, but does not appear to increase the incidence of major bleeding. Unless contraindicated, concomitant administration of ASA is recommended (see DOSAGE AND ADMINISTRATION).

Anticoagulation Treatment Following STREPTASE®

Anticoagulation Following Treatment for Myocardial Infarction: The use of anticoagulants following administration of STREPTASE® treatment for acute myocardial infarction increases the risk of bleeding, and has not been shown to be of unequivocal clinical benefit. Therefore, their use should be decided upon at the discretion of the treating physician.

Anticoagulation Following Intravenous Treatment for Other Indications: To prevent rethrombosis following termination of STREPTASE® infusion treatment for pulmonary embolism or deep vein thrombosis, continuous intravenous infusion of heparin without a loading dose is recommended (see Patient Monitoring).

Patient Monitoring

Intravenous or Intracoronary Artery Infusion for Myocardial Infarction: Intravenous administration of STREPTASE® will cause marked decreases in plasminogen and fibrinogen levels and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT), which usually normalize within 12-24 hours. These changes may also occur in some patients with intracoronary administration of the drug.

Intravenous Infusion for Other Indications: Before commencing thrombolytic therapy, it is desirable to obtain a thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), and a hematocrit and platelet count to obtain hemostatic 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.

During the infusion, decreases in the plasminogen and fibrinogen levels and an increase in the level of 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, or PT, approximately four hours after initiation of therapy.

To prevent rethrombosis following the STREPTASE® infusion, continuous intravenous heparin infusion without a loading dose is recommended. The effect of STREPTASE® on thrombin time (TT) and activated partial thromboplastin time (APTT) will usually diminish within 3 to 4 hours after STREPTASE® therapy. A thrombin time value should be obtained during this period, and heparin therapy without a loading dose can be initiated when TT or APTT is less than twice the normal control value. (See manufacturer's prescribing information for proper use of heparin.) This should be followed by conventional oral anticoagulation therapy.

ADVERSE REACTIONS

The following adverse reactions have been frequently associated with intravenous therapy but may also occur with intracoronary artery infusion of STREPTASE® (streptokinase injection).

Bleeding

The reported incidence of bleeding (major or minor) has varied widely depending on the indication, dose, route and duration of administration and concomitant therapy.

Minor bleeding occurs often with thrombolytic therapy mainly at invaded or disturbed sites. When lytic therapy is continued while local measures are used to control minor bleeding, do not reduce the dose as this will increase the conversion of plasminogen to plasmin which may increase bleeding.

Severe internal bleeding including gastrointestinal and liver hemorrhages, genitourinary, retroperitoneal or rare cases of intracerebral hemorrhages with their complications (also with fatal outcome), may occur, splenic rupture or retroperitoneal hemorrhages have been observed.

Intracerebral bleeding in connection with the treatment of myocardial infarction has been reported with an incidence of 0.1-0.3 %. Several fatalities due to cerebral and other serious internal hemorrhage have occurred during thrombolytic therapy.

In the treatment of acute myocardial infarction with intravenous STREPTASE®, the GISSI and ISIS-2 studies reported a rate of major bleeding (requiring transfusion) of 0.3-0.5%. In the TIMI study, which required both invasive techniques and administration of anticoagulants, a frequency of 15.6% for major bleeding (intracranial, or decrease in hemoglobin >5 g/dl, or decrease in hematocrit >15%) was reported.

During thrombolitic treatment of acute myocardial infarction, hemorrhages into the pericardium including myocardial rupture can occur in individual cases.

Should uncontrollable bleeding occur, STREPTASE® infusion should be terminated immediately; slowing the rate of administration may increase the bleeding. If necessary,

bleeding can be reversed and blood loss effectively managed with appropriate replacement therapy (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Allergic Reactions

If a severe allergic reaction or anaphylactic shock occurs, the infusion should be discontinued immediately.

Immediate reactions:

Reactions attributed to possible anaphylaxis have been observed rarely in patients treated with STREPTASE®. These ranged in severity from minor breathing difficulty, dyspnoea to bronchospasm, periorbital swelling or angioneurotic edema. Other, milder allergic effects such as rash, urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed. Anaphylactoid shock is very rare, having been reported in 0-0.1% of patients.

An anaphylactic reaction has been reported in a patient following a second course of streptokinase within 1 month for clearance of an occluded arteriovenous shunt. Therefore, the possibility of systemic absorption of streptokinase following its use for this purpose must be considered.

Mild or moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of STREPTASE® with adrenergics, antihistamines, or corticosteroids administered intravenously as required.

Late reactions:

In individual cases serum sickness, arthritis, vasculitis, nephritis and neuroallergic symptoms (polyneuropathy, e.g. Guillain Barré syndrome) have been reported in temporal coincidence with streptokinase administration.

Embolisms

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

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

A few cases of cholesterol embolism have been described in temporal coincidence with thrombolytic therapy, particularly in patients undergoing angiography.

Fever

Although STREPTASE® is nonpyrogenic in standard animal tests, approximately one-third of patients treated with STREPTASE® have shown increases in body temperature >0.83°C. Chills may also occur under therapy.

Symptomatic treatment is usually sufficient to alleviate discomfort.

Other

Transient elevations of serum transaminases as well as of bilirubin may occur.

At the beginning of the therapy, a fall in blood pressure, tachycardia or bradycardia (in individual cases reaching as far as shock) are observed occasionally.

In individual cases, under thrombolytic therapy of acute myocardial infarction, rhythm disturbances, persistent angina pectoris as well as cardiac failure reaching as far as cardiac and respiratory arrest may occur. It could be demonstrated, however, that myocardial infarction cardiac arrest due to ventricular fibrillation is more rare in STREPTASE® treated patients than in patients treated conventionally.

In a few instances, after intracoronary thrombolytic therapy in patients with extensive myocardial infarction, non cardiogenic pulmonary edema has been observed.

Individual cases of cerebral convulsion were reported under thrombolytic therapy, and in temporal coincidence with cardiovascular hypoxia and cerebral hemorrhage.

Headache and muscle pain, gastrointestinal complaints, back pain as well as asthenia and malaise may occur under therapy.

Hemorrhagic myocardial infarction has been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Minor bleeding complications with STREPTASE® (streptokinase injection) are usually overcome by increasing the dosage. Should serious uncontrollable bleeding occur as a result of overdosage, the infusion of STREPTASE® and any other concomitant anticoagulant should be discontinued immediately. If necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (fresh blood preferable), packed red cells and cryoprecipitate or fresh frozen plasma. Although the use of aminocaproic acid (or aprotinin) in humans as an antidote for streptokinase has not been documented, it may be considered in an emergency situation.

DOSAGE AND ADMINISTRATION

STREPTASE® (streptokinase injection) should be administered by volumetric infusion pump. Do not use drop-counting infusion methods since STREPTASE® may alter droplet size.

For complete instructions on the reconstitution of the lyophilized product, see PHARMACEUTICAL INFORMATION.

Acute Myocardial Infarction

STREPTASE® treatment of coronary thrombosis should be instituted as soon as possible after the onset of symptoms of acute myocardial infarction. The greatest benefit in mortality reduction was observed when STREPTASE® was administered within 4 hours. The clinical benefit in terms of reduction of mortality could not conclusively be proven in controlled clinical trials in patients being treated beyond 12 hours after the onset of symptoms.

Route	Dosage/Duration
Intravenous infusion (see below)	1,500,000 IU within 60 min.
Intracoronary infusion (see below)	20,000 IU by bolus followed by 2000-4000 IU/min. for 30-90 min. (average 60 min.)

Intravenous Administration: With the above regimen, 1,500,000 IU within 60 minutes, no coagulation tests are necessary to monitor streptokinase therapy. Unless contraindicated, the concomitant use of ASA at a dose of 160 mg/day p.o., starting prior to STREPTASE® infusion and continued for one month is recommended.

Intracoronary Administration: STREPTASE® treatment of coronary thrombosis should be undertaken only in medical centres where coronary arteriography is an established routine and appropriate after-treatment available. STREPTASE® is administered selectively into the thrombosed coronary artery via coronary catheter positioned by the Judkins or Sones technique.
Deep Vein Thrombosis, Pulmonary or Arterial Embolism or Arterial Thrombosis

STREPTASE® treatment should be instituted as soon as possible after onset of thrombotic event, preferably within 7 days. Any delay in instituting lytic therapy to evaluate the effect of heparin therapy decreases the potential for optimal efficacy, although slight enhancement of clot lysis has been shown with initiation of thrombolytic therapy up to 14 days after the onset of symptoms of deep vein thrombosis.

Since human exposure to streptococci is common, antibodies to streptokinase are prevalent. Thus, a loading dose of streptokinase sufficient to neutralize these antibodies is required. A dose of 250,000 IU of STREPTASE® infused into a peripheral vein over 30 minutes has been found appropriate in over 90% of patients. If the thrombin time or any other parameter of fibrinolysis after 4 hours of treatment is not significantly different from the normal control level, discontinue STREPTASE® because excessive resistance to streptokinase is present. Furthermore, if the thrombin time after 16 hours is still prolonged to more than fourfold the control level, the streptokinase dosage should be doubled for several hours until the thrombin time recedes.

The following dosage schedule is recommended:

Indication	Loading Dose	IV Infusion Dose/Duration
Pulmonary Embolism	250,000 IU/ 30 min	100,000 IU/ hr for 24 hrs (72 hrs if concurrent deep vein thrombosis suspected)
Deep Vein Thrombosis	250,000 IU/ 30 min	100,000 IU/hr for 72 hrs
Arterial Thrombosis or Embolism	250,000 IU/ 30 min	100,000 IU/ hr for 24 hrs

A continuous intravenous infusion of heparin, without a loading dose, is recommended to prevent rethrombosis following termination of STREPTASE® infusion (see Patient Monitoring).

Arteriovenous Cannula Occlusion

1. **Before Treatment:** Before using STREPTASE®, an attempt should be made to clear the cannula by careful syringe technique, using heparinized saline solution. If adequate flow is not re-established, STREPTASE® may be employed. Allow the effect of any pretreatment anticoagulants to diminish.

2. **STREPTASE® Administration:** Instill 250,000 IU STREPTASE® in 2 mL intravenous solution into each occluded limb of the cannula slowly. Clamp off cannula limb(s) for 2 hours. Observe the patient closely for possible adverse effects.

3. **After Treatment:** Aspirate contents of infused cannula limb(s), flush with saline, reconnect cannula.

In patients with occlusions of the central retinal vessels a better success rate can be expected if the therapy is started within 6 to 8 hours of arterial occlusions, within 10 days of venous occlusions and within 6 weeks for chronic arterial occlusive diseases (embolic occlusions).

PHARMACEUTICAL INFORMATION

Drug Substance

Streptokinase is a highly purified substance derived from the culture filtrate of **β**-haemolytic streptococci of Lancefield Group C. The molecular weight is 47,000 daltons.

Composition

STREPTASE®, a sterile, white, lyophilized powder, contains: 250,000 IU, 750,000 IU, or 1,500,000 IU of purified streptokinase, 25 mg cross-linked gelatin polypeptides, 25 mg sodium L-glutamate, sodium hydroxide to adjust pH, and 100 mg albumin (human) as stabilizer.

Stability and Storage Recommendations

When stored at room temperature below 25°C, the dried STREPTASE® product is stable up to the expiration date indicated on the package.

Reconstituted and Diluted Solutions

STREPTASE® reconstituted with 5 mL of saline (Sodium Chloride Injection USP, 0.9%) or dextrose (Dextrose Injection USP, 5%) is stable for 24 hours at room temperature (15°- 30°C) and refrigeration (2°- 4°C). For the recommended total period of use of the product, from reconstitution and dilution to the end of patient administration, see 'Diluted Solutions'.

Diluted Solutions

Stability studies have been carried out on the three potencies, reconstituted and diluted with saline (Sodium Chloride Injection USP, 0.9%) or dextrose (Dextrose Injection USP, 5%), to 50 or 500 mL, in glass or plastic containers. The total period of use of the product, from reconstitution and dilution to end of patient administration, should not exceed the specific stability time indicated in Table 2.

Reconstitution and Dilution

Intracoronary Artery and Intravenous Administration

The protein nature and lyophilized form of STREPTASE® require careful reconstitution and dilution.

The following procedure is recommended:

1. Add 5 mL Sodium Chloride Injection USP or Dextrose 5% Injection USP **SLOWLY** to the vacuum packed STREPTASE® container, directing the vehicle at the side of the container rather than into the lyophilized STREPTASE® powder.

2. Roll and tilt the container **GENTLY** to reconstitute. **AVOID SHAKING**. (Shaking may cause foaming.)

3. Dilute the entire reconstituted contents of the container, with Sodium Chloride Injection USP or Dextrose 5% Injection USP, to a total volume of approximately 45 mL (see Table 1). Dilute slowly and carefully; avoid shaking and agitation. (If necessary, total volume may be increased to a maximum of 500 mL with the infusion pump setting in Table 1 increased accordingly.) To facilitate setting the infusion pump rate, a total volume of approximately 45 mL - or multiples thereof - is suggested.

4. Solutions of STREPTASE® reconstituted and diluted to 500 mL or 50 mL with Sodium Chloride Injection, USP, in glass containers, irrespective of which potency is used (250,000 IU; 750,000 IU; 1,500,000 IU), can be drawn through in-line filters without a reduction in drug potency providing the filter is of 0.80 μm or greater pore size (if of cellulose construct) or of 0.22 μm or greater pore size (if of PVC - acrylic polymer construct). Flocculated product should be discarded if filters of the above mentioned construct and/or pore size are not available.

5. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. (The Albumin (Human) may impart a slightly yellow color to the solution.)

6. Do not add other medication to the container of reconstituted STREPTASE®.

For Use in Arteriovenous Cannulae

Slowly reconstitute the contents of 250,000 IU STREPTASE® vial with 2 mL Sodium Chloride Injection USP or Dextrose 5% Injection USP.

SUGGESTED DILUTION AND INFUSION RATES

Table 1. - The suggested dilutions and infusion rates provided in this table represent a practical means of STREPTASE® administration without compromise of safety and efficacy considerations. Depending on the type of available infusion pump/bags, the solution/volume/rates cited may be adjusted to correspond with the particular dosage rate to be administered.

Indication/ Dosage Route	Total dose to be administered (IU)	Total vials or bottles of STREPTASE® required		Volume of dilution per vial or bottle (mL)	LOADING		MAINTENANCE	
					Loading Dose (IU)	Infusion Rate (mL/hr)	Maintenance Dose (IU)	Infusion Rate (mL/hr)
I. Acute Myocardial Infarction								
A. Intracoronary Artery Administration	140,000 IU	1 vial	250,000 IU	125	20,000 IU	10 mL bolus injection	2,000 IU/min	60 mL/hr
B. Intravenous Administration	1,500,000 IU	I) 1 vial II) 1 bottle III) 2 vials	1,500,000 IU 1,500,000 IU 750,000 IU	50* 50* 50*	--- 	--- 	1,500,000 IU " "	i) 50 mL/hr ii) 50 mL/hr iii) 100 mL/hr
II. Deep Vein Thrombosis, Pulmonary Embolism, Arterial Thrombosis								
A. Intravenous Infusion	2,650,000 to 7,450,000 IU	I) 11 to 30 vials ii) 4 to 10 vials iii) 2 to 5 vials iv) 2 to 5 bottles	250,000 IU 750,000 IU 1,500,000 IU 1,500,000 IU	45** 45** 45** 45**	250,000 IU " " "	i)90 mL/hr for 30 min ii)30 mL/hr for 30 min iii)15 mL/hr for 30 min iv)15 mL/hr for 30 min	100 000 IU/hr for 24 to 72 hr " " " "	i)18 mL/hr ii)6.0 mL/hr iii)3.0 mL/hr iv)3.0 mL/hr

*   Volumes of solution of 50 to 250 mL have been used [49,50,51]

**   If necessary, total volume may be increased, in increments of approximately 45 mL, to a maximum of 500 mL with the infusion pump rate adjusted accordingly. The total volume of approximately 45 mL or multiple thereof is recommended to facilitate setting the infusion pump for hourly dosage.

TABLE 2

Stability of Reconstituted/Diluted Solutions

DOSE (IU)	FINAL VOLUME (mL)	DILUENT	CONTAINER	TEMPERATURE	STABLE (hours)
250,000	50	saline or dextrose	plastic	RT*	24
	500	dextrose	glass	RT	12
	500	dextrose	glass	5 °C	24
	500	dextrose	plastic	RT	12
	500	dextrose	plastic	5 °C	24
750,000	50	dextrose	glass or plastic	RT	24
	50	dextrose	glass or plastic	5 °C	24
	50	saline	plastic	RT	24
1,500,000	50	saline or dextrose	glass or plastic	RT	24
	500	saline or dextrose	glass	RT	24

* Room temperature

AVAILABILITY OF DOSAGE FORMS

STREPTASE® (streptokinase injection) is supplied as a sterile, lyophilized, white powder in 6.5 mL vials (250,000 IU, 750,000 IU and 1,500,000 IU) or 68 mL infusion bottles (1,500,000 IU). The container labels are color-coded, corresponding to the amount of purified streptokinase in each vial:

green
    packages of 10   250,000 IU   6.5 mL vial

blue
    packages of 10   750,000 IU   6.5 mL vial

red
    packages of 10   1,500,000 IU   6.5 mL vial

red
    packaged individually   1,500,000 IU   68 mL infusion bottle

PHARMACOLOGY

Streptokinase is a bacterial protein elaborated by group C ß-haemolytic streptococci.

Plasminogen is first converted to plasmin (fibrinolysin) which occurs in two steps. One mole of streptokinase combines with one mole of plasminogen to produce the "activator complex". The activator then catalyzes the conversion of the remaining plasminogen into plasmin. Plasmin catalyzes the hydrolysis of fibrin into several soluble peptide fragments. Since plasminogen is present in the thrombus/embolus, activation by streptokinase occurs within the thrombus/embolus as well as on its surface.

These reactions depend on the concentration of streptokinase. At a molar ratio of plasminogen to streptokinase of 10:1, maximal amounts of plasmin are formed, whereas equimolar proportions produce maximal amounts of activator. Consequently when small amounts of streptokinase are added to a given quantity of plasminogen, high levels of plasmin are produced and little activator, whereas when large amounts of streptokinase are added, small amounts of plasmin are produced and large amounts of activator.

It is known from the biochemical findings outlined above and from clinical data that high doses of streptokinase produce mainly activator in the blood stream and relatively little plasmin. The low but measurable plasmin concentration in the circulating blood minimizes the risk of both, hemorrhage during treatment and rethrombosis after treatment.

The half-life of the activator complex is about 23 minutes; the complex is inactivated, in part, by streptococcal antibodies. The mechanism by which dissociated streptokinase is eliminated is clearance by sites in the liver; however, no metabolites of streptokinase have been identified.

Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins. Plasmin is inactivated by circulating inhibitors, such as alpha-2-plasmin inhibitor or alpha-2-macroglobulin. These inhibitors are rapidly consumed at high doses of streptokinase.

Intravenous infusion of streptokinase is followed by increased fibrinolytic activity, which decreases plasma fibrinogen levels for 24 to 36 hours. The decrease in plasma fibrinogen is associated with decreases in plasma and blood viscosity and red cell aggregation. The hyperfibrinolytic effect disappears within a few hours after discontinuation, but a prolonged thrombin time may persist for up to 24 hours due to the decrease in plasma levels of fibrinogen and an increase in the amount of circulating fibrin(ogen) degradation products (FDP). Depending upon the dosage and duration of infusion of streptokinase, the thrombin time will decrease to less than two times the normal control value within 4 hours, and return to normal by 24 hours.

Intravenous administration has been shown to reduce blood pressure and total peripheral resistance with a corresponding reduction in cardiac afterload. These expected responses were not studied with the intracoronary administration of STREPTASE®. The quantitative benefit has not been evaluated.

Two large, randomized, multicentre, placebo-controlled studies involving almost 30,000 patients have demonstrated that a 60-minute intravenous infusion of 1,500,000 IU of STREPTASE® (streptokinase injection) significantly reduces mortality following a myocardial infarction. One of these studies also evaluated concomitant oral administration of low-dose ASA (160 mg/ day for one month).

In the GISSI study, the reduction in mortality was dependent on the time after the onset of symptoms at which the drug was administered. There was a 47% reduction in mortality among patients treated within one hour of the onset of chest pain, a 23% reduction among patients treated within 3 hours and a 17% reduction in patients treated after 3-6 hours. There was also a reduction (statistically not significant) in mortality in patients treated 6-12 hours from the onset of symptoms.

In the ISIS-2 study, the reduction in mortality was also dependent on the duration of the interval between the onset of symptoms and the time of administration of the drug. Administration of STREPTASE® or ASA within the first hour after the onset of symptoms resulted in a reduction in mortality of 44%. Concomitant administration of both drugs resulted in a further reduction in mortality (53% if administered within the first four hours, compared to 35% reduction for streptokinase alone administered within 4 hours). The additional benefit was still significant when treatment was started 5-24 hours after the onset of symptoms (33% for the combined therapy, 17% for streptokinase alone). Overall, in the 0-24 hour time period there was a 42% reduction in the odds of death following combined treatment (STREPTASE® and ASA) as compared to placebo (2p<0.00001) and a 25% reduction in the odds of death with streptokinase alone versus placebo (2p<0.00001).

A smaller study involving 368 patients receiving intravenous streptokinase (1,500,000 IU over one hour) or standard therapy showed that the streptokinase group mortality was significantly

lower (6.3% vs 9.6%) at 14 days post-MI. Long-term survival for patients with anterior infarction was significantly improved; 2-year survival was 81% (streptokinase) and 65% (controls).

Studies measuring left ventricular ejection fraction (LVEF) at discharge showed the mean LVEF were 3-6 percentage points higher in the streptokinase group than in the control group. This difference was statistically significant in some of the studies. Furthermore, some studies reported greater improvement in LVEF among patients treated within 3 hours than in patients treated later following the onset of symptoms.

Results from three independent randomized controlled trials show that, following treatment with i.v. streptokinase, there is a reduction in the number of patients with clinical congestive heart failure, a reduction in the number of patients with reduced myocardial function leading to symptomatic congestive heart failure, and a reduction in the number of deaths due to congestive heart failure.

One study showed that clinical congestive heart failure occurred in 12.8% of streptokinase-treated patients, compared to 15% of the control patients (p<0.001). Two studies showed a reduction in deaths from congestive heart failure. One showed that after 30 days of treatment, 1.9% of the streptokinase patients died, as compared to 7.1% in the placebo group. The other showed a reduction from 4.0% in the control group to 2.9% in the streptokinase group.

The rate of reocclusion of the infarct-related vessel has been reported to be approximately 15-20%. The rate of reocclusion depends on dosage, additional anticoagulant therapy and residual stenosis. In the ISIS-2 study, it was shown that an increase in reinfarction can be avoided when STREPTASE[®] is combined with ASA. The rate of reinfarction in the combination group was 1.8%.

STREPTASE[®] administered by the intracoronary route has resulted in thrombolysis usually within one hour, and ensuing reperfusion results in limitation of the infarct size, improvement of cardiac function and reduction in mortality. LVEF was increased in patients treated with streptokinase when compared to patients treated with conventional therapy. When the initial LVEF was low, the STREPTASE[®]-treated patients showed greater improvement than the controls. Spontaneous reperfusion is known to occur and has been observed with angiography at various time points after infarction. Data from one study show that 73% of the STREPTASE[®] and 47% of the placebo-allocated patients reperfused during hospitalization.

Studies with thrombolytic therapy for pulmonary embolism show no significant difference in lung perfusion scan between the thrombolysis group and the heparin group at one-year follow-up. However, measurements of pulmonary capillary blood volumes and diffusing capacities at 2 weeks and 1 year after therapy indicate that a more complete resolution of thrombotic obstruction and normalization of pulmonary physiology was achieved with thrombolytic therapy, thus preventing the long-term sequelae of pulmonary hypertension and pulmonary failure.
The long-term benefit of STREPTASE[®] therapy for deep vein thrombosis (DVT) has been evaluated venographically. The combined results of five randomized studies show no residual thrombotic material in 60-75% of patients treated with STREPTASE[®] versus 10% of those

treated with heparin. Studies have demonstrated a better salvage of valvular function and prevention of postphlebitic syndrome by the combined usage of STREPTASE® and heparin than by heparin alone.

In the management of peripheral arterial thromboembolism, there is a time-related decrease in effectiveness when STREPTASE® is used. When administered 3-10 days after the onset of obstruction, rates of clearance of 50-75% were reported.

TOXICOLOGY

Acute Toxicity

1. **Mice**

Male and female mice, weighing approximately 20 g each, were divided into 4 groups of 10 animals. After dilution in saline intravenous doses of 12.5×10^6, 25.0×10^6 and 37.5×10^6 IU/kg of streptokinase were given as a single dose to 3 groups, and the last group received an injection of saline. The injected volume ranged from 0.4 to 1.1 mL. There were no signs of toxicity and no deaths during the following 7 days of observation. Therefore, the LD_{50} in mice is greater than 37,500 000 IU/kg.

2. **Guinea Pigs**

Male and female guinea pigs, weighing approximately 330 g each, were divided into 4 groups of 10 animals. The intravenous doses of streptokinase after dilution in saline were 0.75×10^6, 1.5×10^6, and 2.25×10^6 IU/kg. The last group received an injection of saline. The injected volume ranged from 0.3 to 1.1 mL. During 7 days of observation there were no signs of toxicity and no deaths. Therefore, the LD_{50} in guinea pigs is greater than 2,250,000 IU/kg.

3. **Rabbits**

Male and female rabbits, weighing approximately 2 kg each, were divided into 3 groups of 10 animals. The intravenous doses of streptokinase after dilution in saline were 0.5×10^6 and 0.75×10^6 IU/kg. The control group received an injection of saline of equal volume (i.e., 15 mL). The volume of injection was approximately 15 mL. Three animals in the higher dosage group lost weight. One animal of this group died on the 8th day. Therefore, the LD_{50} in rabbits is greater than 750,000 IU/kg.

Subacute Toxicity

1. **Rats**

Streptokinase in physiological saline was given intravenously at doses of 120,000, 300,000 and 900,000 IU/kg to groups of 10 males and 10 females, weighing between 160 and 321 g, on 14 consecutive days. A control group was given saline in equal volume. There were no significant drug effects on clinical condition, body weight, food consumption, hematology, urinalysis and clinical chemistry, or at necropsy, including organ weights and histopathology. The following statistically significant differences (within the normal range) were considered incidental and not drug related. The mean values of total cholesterol of the males in all dosage groups were higher than in the controls; the mean value of inorganic phosphorus in the female rats of the highest dosage group was higher than in the controls.

2. Dogs

Streptokinase was given intravenously in physiological saline in doses of 60,000, 150,000 and 450,000 IU/kg to groups of 3 male and 3 female Beagle dogs, weighing between 6.8 and 10.4 kg on 14 successive days. The control group received 1.2 mL/kg of saline. There were no adverse effects on clinical condition, body weight, food consumption, rectal body temperature, hematology, urinalysis and clinical chemistry, or at necropsy, including organ weights and histopathology. Small statistically significant differences were observed in the number of leukocytes and in a few parameters of blood chemistry, but these were considered to be biologically insignificant and not related to the drug, since they remained within the normal limits.

Additional Studies

1. **Local Tolerance (rabbit ear vein)**

Streptokinase (750,000 IU in 15 mL of physiological saline) was infused over 3 hours into the partially occluded left lateral ear vein of 4 rabbits. Fifteen mL of physiological saline was infused in 2 control rabbits under the same conditions. The animals were killed 2 hours after the completion of the infusion and the ear veins dissected. There was no thrombosis or inflammatory reaction.

2. **Human Blood *In Vitro***

Human blood of 3 healthy males was studied for *in vitro* compatibility with streptokinase dissolved in 5% dextrose or saline. The parameters observed were total red blood cell count, hematocrit, hemoglobin, mean corpuscular volume, erythrocyte sedimentation rate, blood pH, total leukocyte count, differential count, and erythrocyte and platelet morphology; the blood was 2-42 hours old. The concentrations of streptokinase were 200 and 1000 IU/mL of whole blood, which is comparable to therapeutic doses of 1,000,000 and 5,000,000 IU, respectively,

given to a man with 5 litres of blood. There were no deleterious effects on any of the parameters studied. The erythrocyte sedimentation rate was lower in the presence of streptokinase than in its absence.

3. Body Temperature in Rabbits

In rabbits immunized with streptokinase, but not in normal rabbits, streptokinase injection can produce a rise in body temperature. Neutralization of the streptokinase antibodies prevented the rise in temperature.

During the lysis of thrombi induced by thrombin in the ear vein of rabbits, a rise in body temperature was obtained during the streptokinase infusion and during treatment with a thrombolytic gel. Untreated control animals also showed a rise in temperature during thrombolysis. Thus, fever may be both the result of thrombolysis or an allergic phenomenon. Pyrogenic substances had been excluded as a cause of the fever.

REFERENCES

1. Alkjaersig N, Fletcher AP, Sherry S. The mechanism of clot lysis by plasmin. J Clin Invest 1959; 38:1086-1095.
2. Amery A, Deloof W, Vermylen J *et al*. Outcome of recent thromboembolic occlusions of limb arteries treated with streptokinase. Br Med J 1970; 4:639-644.
3. Anderson JL, Marshall HW, Bray BE, *et al*. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983; 308:1312-1318.
4. Arnesen H, Hoiseth A, Ly B. Streptokinase or heparin in the treatment of deep vein thrombosis - follow-up results of a prospective study. Acta Med Scand 1982; 211:65-68.
5. Arnesen H, Heilo A, Jakobsen E, *et al*. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. Acta Med Scand 1978; 203:457-463.
6. Bell WR, Meak AG. Guidelines for the use of thrombolytic agents. N Engl J Med 1979; 301:1266-1270.
7. Brogden RN, Speight TM, Avery GS. Streptokinase: a review of its clinical pharmacology, mechanism of action and therapeutic uses. Drugs 1973; 5:357-445.
8. Chesterman CN, Allington MJ, Sharp AA. Relationship of plasminogen activator to fibrin. Nature (New Biology) 1972; 238:15-17.
9. Common HH, Seaman AJ, Rosch J, *et al*. Deep vein thrombosis treated with streptokinase or heparin. Follow-up of a randomized study. Angiology 1976; 27:645-654.
10. Cowley MJ, Hastillo A, Vetrovec GW, *et al*. Effects of intracoronary streptokinase in acute myocardial infarction. Am Heart J 1981; 102:1149-1158.
11. Cowley MJ, *et al*. Fibrinolytic effects of low dose intracoronary streptokinase infusion in acute myocardial infarction. In: Trubestein G, Etzel F, eds. Fibrinolytic therapy. F.K. Schattauer Verlag Stuttgart/New York, 1983, pp. 489-496.
12. De Wood MA, Spores J, Notske R, *et al*. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. New Engl J Med 1980; 303:897-902.
13. Dotter CT, Rosch J, Seaman AJ, *et al*. Streptokinase treatment of thromboembolic disease. Radiology 1972; 102:283-290.

14. Eden KV. Possible association of Guillain-Barre Syndrome with thrombolytic therapy. JAMA 1983; 249(15):2020-2021.

15. Elliott MS, Immelman EJ, Jeffery P, *et al*. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. Br J Surg 1979; 66:838-843.

16. Fears R et al. Monitoring of streptokinase resistance titre in acute myocardial infarction patients up to 30 months after giving streptokinase or anistreplase and related studies to measure specific antistreptokinase IgG. Br Heart J. 1992;68:167-170.

17. Fletcher AP, Alkjaersig N, Sherry S. The clearance of heterologous proteins from the circulation of normal and immunized man. J Clin Invest 1958; 37:1306-1315.

18. Fratantoni JC, Ness P, Simon TL. Thrombolytic therapy: current status. N Engl J Med 1975; 293:1073-1078.

19. Furberg CD. Clinical value of intracoronary streptokinase. Am J Cardiol 1984; 53(4):626-627. (Editorial)

20. Ganz W. Intracoronary thrombolysis in acute myocardial infarction. Am J Cardiol 1983; 52(3):92A-95A.

21. GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'infarcto miocardico). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; *i*:397-402.

22. GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'infarcto miocardico). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Lancet 1987; *ii*:871-874.

23. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; *ii*:349-360.

24. Johansson L, Nylander G, Hedner U, *et al*. Comparison of streptokinase with heparin: late results in the treatment of deep venous thrombosis. Acta Med Scand 1979; 206:93-98.

25. Kakkar VV. Results of streptokinase therapy in deep venous thrombosis. Postgrad Med J 1973; (August Suppl): 60-64.

26. Kennedy JW, Martin GV, Davis KB, *et al*. The Western Washington intravenous streptokinase in acute myocardial infarction randomized trial. Circulation 1988; 77(2):345-352.

27. Kennedy JW, Ritchie JL, Davis KB, *et al*. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. New Engl J Med 1985; 312:1073-1078.

28. Kennedy JW, Ritchie JL, Davis KB, *et al*. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. New Engl J Med 1983; 309(24):1477-1482.

29. Ludwig H. Results of streptokinase therapy in deep vein thrombosis during pregnancy. Postgrad Med J 1973; 49(Suppl 5): 65-67.

30. Marder VJ, Sherry S. Thrombolytic therapy: current status. New Engl J Med 1988; 318(23):1512-1520.

31. Marder VJ. The use of thrombolytic agents: choice of patient, drug administration, laboratory monitoring. Ann Intern Med 1979; 90(5):802-808.

32. Marder VJ, Soulen RL, Atichartakarn V, *et al*. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89(5):1018-1029.

33. Martin TR, Sandblom RL, Johnson RJ. Adult respiratory distress syndrome following thrombolytic therapy for pulmonary embolism. Chest 1983; 83(1):151-153.

34. Mathey DG, Schofer J, Kuck K-H, *et al*. Transmural, haemorrhagic myocardial infarction after intracoronary streptokinase. Clinical, angio-graphic, and necropsy findings. Br Heart J 1982; 48:546-551.

35. Mathey DG, Kuch KH, Tilsner V, *et al*. Nonsurgical coronary artery recanalization in acute transmural myocardial infarction. Circulation 1981; 63(3):489-497.

36. Mathey DG, Rodewald G, Rentrop P, *et al*. Non-surgical coronary artery recanalisation and bypass grafting of the remaining stenosis - a complementary approach to reduce infarct size and prevent reinfarction. Am Heart J 1981; 102:1194-1201.

37. McNicol GP. The fibrinolytic system. Postgrad Med J 1973; 49(August Suppl): 10-12.

38. Merx W, Dorr R, Rentrop P, *et al*. Intracoronary infusion of streptokinase in acute myocardial infarction. Postacute management and hospital course in 204 patients. Am Heart J 1981; 102:1181-1187.

39. Persson AV, Thompson JE, Patman RD. Acute arterial occlusions. Vasc Surg 1977; 11(6):359-363.

40. Rao AK, Pratt C, Berke A, *et al*. Thrombolysis in myocardial infarction (TIMI) trial - phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988; 11(1):1-11.

41. Reduto LA, Freund GC, Gaeta JM, *et al*. Coronary artery reperfusion in acute myocardial infarction: beneficial effects of intracoronary streptokinase upon left ventricular performance. Am Heart J 1981; 102:1168-1177.

42. Reduto LA, Smalling RW, Freund GC, *et al*. Intracoronary infusion of streptokinase in patients with acute myocardial infarction: effects of reperfusion on left ventricular performance. Am J Cardiol 1981; 48(3):403-409.

43. Reichle FA, Rao NA, Chang KH, *et al*. Thrombolysis of acute or subacute nonembolic arterial thrombosis. J Surg Res 1977; 22(3):202-208.

44. Rentrop KP, Karsh KR, Blanke H, *et al*. Changes of left ventricular function after non-surgical reperfusion in evolving myocardial infarction. Am Heart J 1981; 102:1188-1193.

45. Rentrop P, Blanke H, Karsh KR, *et al*. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981; 63(2):307-317.

46. Rutsch W, Schartl M, Mathey D, *et al*. Percutaneous transluminal coronary recanalization: procedure, results and acute complications. Am Heart J 1981; 102:1178-1181.

47. Sasahara AA, Hyers TM, Cole CM, *et al*. The urokinase pulmonary embolism trial. Circulation 1973; 47(Suppl II): 1-108.

48. Schaer DH, Ross AM, Wasserman AG. Reinfarction, recurrent angina, and reocclusion after thrombolytic therapy. Circulation 1987; 76(suppl II): 57-62.

49. Schreiber T. Review of clinical studies of thrombolytic agents in acute myocardial infarction. Amer J Med 1987; 83(suppl 2A): 20-25.

50. Schroeder R, Biamino G, v. Leitner ER, *et al*. Intravenous short-term infusion of streptokinase in acute myocardial infarction. Circulation 1983; 67(3):536-548.

51. Schwarz F, Schuler G, Katus H, *et al*. Intracoronary thrombolysis in acute myocardial infarction: duration of ischemia as a major determinant of late results after recanalization. Am J Cardiol 1982; 50(5):933-937.
52. Seaman AJ, Common HH, Rosch J, *et al*. Deep vein thrombosis treated with streptokinase or heparin: a randomized study. Angiology 1976; 27:549-556.
53. Sharma GVRK, Burleson VA, Sasahara AA. Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 1980; 303(15):842-845.
54. Sherry S, Bell WR, Duckert FH, *et al*. Thrombolytic therapy in thrombosis: A National Institutes of Health Consensus Development Conference. Ann Intern Med 1980; 93:141-144.
55. Sherry S. Streptokinase and urokinase. Modern Med 1976; 44:72-75.
56. Smalling RW, Fuentes F, Matthews MW, *et al*. Sustained improvement in left ventricular function and mortality by intracoronary streptokinase administration during evolving myocardial infarction. Circulation 1983; 68(1):131-138.
57. Swan HJC. Thrombolysis in acute evolving myocardial infarction: a new potential for myocardial salvage. N Engl J Med 1983; 308:1354-1355. (Editorial)
58. The I.S.A.M. Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). N Engl J Med 1986; 314(23):1465-1471.
59. Urokinase Pulmonary Embolism Study Group. Urokinase-Streptokinase embolism trial. JAMA 1974; 229:1606-1613.
60. Urokinase Pulmonary Embolism Trial Study Group: A urokinase pulmonary embolism trial. A national cooperative study. Circulation 1973; 47(Suppl II):1-108.
61. White HD, Norris RM, Brown MA, *et al.* Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Eng J Med 1987; 317(14):850-855.
62. Yusuf S, Collins R, Peto R, *et al.* Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: Overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. Eur Heart J 1985; 6:556-585.