

### 1.3.1.1.b Text SPC 1 500 000 IU

#### SUMMARY OF PRODUCT CHARACTERISTICS



#### 1 NAME OF THE MEDICINAL PRODUCT

Fibrion 1 500 000 Powder for solution for infusion

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fibrion 1 500 000 is presented as a powder for solution in vials containing 1.5 million 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

Fibrion is indicated in adults.

Acute myocardial infarction: within 12 hours of onset with persistent ST-segment elevation or recent left bundle-branch block. Note: No statement on therapy outcome can be made for administration beyond the time window indicated above.

##### 4.2 Posology and method of administration

###### Posology

###### *Paediatric population*

The safety and efficacy of Fibrion in children, infants and neonates have not been established. The benefit of treatment has to be evaluated against the potential risks, which may aggravate an acute life-threatening condition (see section 4.4).

###### Method of Administration

The administration of streptokinase is intravenous.

###### *Adults*

Systemic administration: A single dose of 1.5 million IU streptokinase should be infused intravenously over one hour.

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 fibrinolitics should be used (see sections 4.4 and 4.8).

#### *Adjuvant treatment*

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

### **4.3 Contraindications**

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

Contraindications to treatment with Fibrion, 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 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 operations (6<sup>th</sup> to 10<sup>th</sup> 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 fibrillation
- aortic dissection
- 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 as 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.

#### Simultaneous treatment with acetylsalicylic acid

Recent evidence indicates that controlled-dose adjuvant acetylsalicylic therapy in combination with streptokinase is capable of improving the response in the management of acute myocardial infarction. See also section 4.2.

#### 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.

#### 4.6 Fertility, pregnancy and lactation

Fibrin 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 than 1/10                                |
| 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 than 1/10,000 (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 antifibrinolitics is recommended. If necessary, clotting factors can be substituted. Additional administration of synthetic antifibrinolitics 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/iritocyclitis

#### 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.



#### **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

Fibrion activates the intrinsic fibrinolytic system 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.

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-plasminogen 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 Fibrion, no evidence of mutagenic potential was found. No other preclinical safety studies have been performed on Fibrion.

### **6 PHARMACEUTICAL PARTICULARS**

#### **6.1 List of excipients**

Human albumin, Aminoacetic acid (glycine), Mannitol



## 6.2 Incompatibilities

No incompatibilities have been reported when Fibrion 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 Fibrion 1 500 000 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

Fibrion 1 500 000 is supplied in 10 ml glass vials with rubber closures and aluminium seal with plastic flip-top caps.

Fibrion 1 500 000 is available in packages containing one vial.

## 6.6 Special precautions for disposal and other handling

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.

Fibrion may be given by intravenous infusion in 50-200 ml of physiological saline, 5% glucose solution, 5% fructose solution, or Ringer-lactate solution.

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

## 7 MANUFACTURER

Lyocontract GmbH

Pulverwiese 1, Trift, Ilsenburg, D-38871, Germany

For:

Biofactor GmbH

Rudolf-Huch-Str. 14, D-38667 Bad Harzburg, Germany

Imported by:

PT Dexa Medica

Jl. Jend. Bambang Utoyo No. 138

Palembang - Indonesia

## 8 MARKETING AUTHORISATION NUMBER(S)

NA

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

NA

## 10 DATE OF REVISION OF THE TEXT

06/2015