Contents

Summary of Product Characteristic

1. Name of the Medicinal Product

1.1 Product Name: Elaxim 30/Elaim 40/ Elaxim

1.2 Strength:

One vial of Elaxim 30 contains 30 mg Tenecteplase

One vial of Elaxim 40 contains 40 mg Tenecteplase

One vial of Elaxim contains 52.5 mg Tenecteplase

1.3 Dosage Form: Elaxim 30/Elaxim 40/ Elaxim is supplied as a sterile, lyophilized powder in a vial under partial vacuum. Each vial of Elaxim 30/Elaxim 40/ Elaxim is packaged with one 06 mL, 08 mL and 10 mL vial of Sterile Water for Injection, for reconstitution respectively. Reconstituted Tenecteplase should be administered as a single IV bolus over 5 seconds.

2. Quality and Quantitative Composition

Each vial of Elaxim 30 contains:

Recombinant Tissue Plasminogen Activator (TNK-t-PA)…… 30 mg

As lyophilized powder to be reconstituted with 06 ml of Sterile Water for Injection.

Each vial of Elaxim 40 contains:

Recombinant Tissue Plasminogen Activator (TNK-t-PA)…… 40 mg

As lyophilized powder to be reconstituted with 08 ml of Sterile Water for Injection

Each vial of Elaxim contains:

Recombinant Tissue Plasminogen Activator (TNK-t-PA)…… 52.5* mg

As lyophilized powder to be reconstituted with 10 ml of Sterile Water for Injection

(*5% overages are added to compensate process loss)

For full list of excipients please refer section 6.1.

3. Pharmaceutical Form

Powder and solvent for solution for injection.

Elaxim 30/40/52.5 is a sterile, white to off-white, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with Sterile Water for Injection (SWFI).

4. Clinical Particulars:

4.1 Therapeutic indications

Tenecteplase is indicated in adults for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Posology

Tenecteplase should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with tenecteplase should be initiated as early as possible after onset of symptoms.

Elaxim should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
For details see section 6.6: Special precautions for disposal and other handling			

Elderly (≥ 75 years)

Tenecteplase should be administered with caution in the elderly (≥ 75 years) due to a higher bleeding risk

Paediatric population

The safety and efficacy of tenecteplase in children (below 18 years) have not been established. No data are available.

Renal and hepatic impairment

There is no guidance for the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency, as the effect of renal and hepatic dysfunction on tenecteplase has not been studied.

Method of administration

The product should be visually inspected prior to administration for particulate matter and discoloration. Tenecteplase may be administered as reconstituted at 5mg/mL. Precipitation may occur when tenecteplase is administered in an IV line containing dextrose. Dextrose-containing lines should be flushed with a saline-containing solution prior to and following single bolus administration of tenecteplase.

Reconstituted tenecteplase should be administered as a single IV bolus over 5 seconds. Because tenecteplase contains no antibacterial preservatives, it should be reconstituted immediately before use. If the reconstituted tenecteplase is not used immediately, refrigerate the tenecteplase vial at 2 to 8°C (36–46°F) and use within 8 hours.

Adjunctive therapy

Antithrombotic adjunctive therapy with platelet inhibitors and anticoagulants should be administered according to the current relevant treatment guidelines for the management of patients with ST-elevation myocardial infarction.

For coronary intervention see section 4.4.

Unfractionated heparin and enoxaparin have been used as antithrombotic adjunctive therapy in clinical studies with tenecteplase.

Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued with lifelong treatment unless it is contraindicated.

4.3 Contraindications

Tenecteplase must not be administered to patients with a history of an anaphylactic (i.e. life-threatening) reaction to any of the constituents (i.e. tenecteplase or any excipient) or gentamicin (a trace residue from the manufacturing process). If treatment with tenecteplase is nevertheless considered to be necessary, facilities for resuscitation should be immediately available in case of need.

Furthermore, tenecteplase is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (INR > 1.3) (see section 4.4, subsection "Bleeding").
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis
- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of haemorrhagic stroke or stroke of unknown origin
- Known history of ischaemic stroke or transient ischaemic attack in the preceding 6 months.
- Dementia.

4.4 Special warning and precautions for use

Coronary intervention

If primary percutaneous coronary intervention (PCI) is scheduled according to the current relevant treatment guidelines, tenecteplase should not be given.

Patients who cannot undergo primary PCI within one hour as recommended by guidelines and receive tenecteplase as primary coronary recanalization treatment should be transferred without delay to a coronary intervention capable facility for angiography and timely adjunctive coronary intervention within 6-24 hours or earlier if medically indicated.

Bleeding

The most common complication encountered during tenecteplase therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during tenecteplase therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cut down sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with tenecteplase.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. In the following conditions, the risk of tenecteplase therapy may be increased and should be weighed against the anticipated benefits:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. patients over 75 years
- Low body weight < 60 kg.
- Patients receiving oral anticoagulants: The use of tenecteplase may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely and if appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity on the coagulation system (e.g. INR ≤ 1.3 for vitamin K antagonists

or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) is available when tenecteplase is administered.

GPIIb/IIIa antagonists

Concomitant use of GPIIb/IIIa antagonists increases bleeding risk.

Hypersensitivity/Re-administration

No sustained antibody formation to the tenecteplase molecule has been observed after treatment. However, there is no systematic experience with re-administration of tenecteplase. Caution is needed when administering tenecteplase to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, or to gentamicin (a residue from the manufacturing process). If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, tenecteplase should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

Paediatric population

Tenecteplase is not recommended for use in children (below 18 years) due to a lack of data on safety and efficacy.

4.5 Interaction with other medicinal products and other forms of interactions

No formal interaction studies with tenecteplase and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant

interactions with medicinal products commonly used in patients with AMI and concomitantly used with tenecteplase.

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after tenecteplase therapy.

Concomitant use of GPIIb/IIIa antagonists increases bleeding risk.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There is limited amount of data from the use of tenecteplase in pregnant women. Nonclinical data performed with tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the active substance and in a few cases abortion and resorption of the foetus occurred (effects only have been observed with repeated dose administration). Tenecteplase is not considered to be teratogenic.

The benefit of treatment must be evaluated against the potential risks in case of myocardial infarction during pregnancy.

Breast-feeding

It is not known whether tenecteplase is excreted in human milk.

Caution should be exercised when tenecteplase is administered to a nursing woman and a decision must be made whether breast-feeding should be discontinued within the first 24 hours after administration of tenecteplase.

Fertility

Clinical data as well as nonclinical studies on fertility are not available for tenecteplase.

4.7 Effects on ability to drive and use machine

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Haemorrhage is a very common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Death and permanent

disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 1 displays the frequency of adverse reactions

System Organ Class	Adverse Reaction
Immune system disorders	
Rare	Anaphylactoid reaction (including rash, urticaria, bronchospasm, laryngeal oedema)
Nervous system disorders	
Uncommon	Intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage) including associated symptoms as somnolence, aphasia, hemiparesis, convulsion
Eye disorders	
Uncommon	Eye haemorrhage
Cardiac disorders	

Uncommon	Reperfusion arrhythmias (such as asystole, accelerated idioventricular arrhythmia, arrhythmia, extrasystoles, atrial fibrillation, atrioventricular first degree to atrioventricular block complete, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with tenecteplase.
Rare	Pericardial haemorrhage
Vascular disorders	
Very common	Haemorrhage
Rare	Embolism (thrombotic embolisation)
Respiratory, thoracic and mediastinal disorders	
Common	Epistaxis
Rare	Pulmonary haemorrhage
Gastrointestinal disorders	
Common	Gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage)
Uncommon	Retroperitoneal haemorrhage (such as retroperitoneal haematoma)
Not known	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Common	Ecchymosis
Renal and urinary disorders	
Common	Urogenital haemorrhage (such as haematuria, haemorrhage urinary tract)
General disorders and administration site conditions	
Common	Injection site haemorrhage, puncture site haemorrhage

Investigations	
Rare	Blood pressure decreased
Not known	Body temperature increased
Injury, poisoning and procedural complications	
Not known	Fat embolism, which may lead to corresponding consequences in the organs concerned

As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common: hypotension, heart rate and rhythm disorders, angina pectoris
- common: recurrent ischaemia, cardiac failure, myocardial infarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon: cardiac arrest, mitral valve incompetence, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare: pulmonary embolism

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

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 to safety.ROW@emcure.com.

4.9 Overdose

Symptoms

In the event of overdose there may be an increased risk of bleeding.

Therapy

In case of severe prolonged bleeding substitution, therapy may be considered (plasma, platelets), see also section 4.4.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antithrombotic agents, enzymes; ATC code: B01A D11

Mechanism of action

Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects

After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Preclinical Study

Comparative *in-vivo* study of pharmacological activity of tenecteplase and Metalyse

The *in vivo* pharmacodynamics of the intravenous tenecteplase (Elaxim, test drug) and intravenous Metalyse® (reference drug), were compared using common carotid artery thrombosis model in rabbits in a study conducted in Russian Federation. The data showed that administration of study drugs resulted in decrease in concentrations of fibrinogen and activity of alpha-2 anti-plasminogen along with trend to increase in activity of plasminogen. No signs of thrombi were observed in animals who received the maximum dose of the study drugs. No effect on activated partial thromboplastin time (aPTT) and prothrombin time (PT) was noted. The test and reference product showed comparable therapeutic responses in the animal model

Comparative *In-Vitro* study of Pharmacological Activity of drug Tenecteplase and drug Metalyse registered in the Russian federation

Performed comparative study of pharmacological activity of drug Tenecteplase, lyophilisate for preparation of solution for intravenous administration 10,000 units (50 mg) (JSC PHARMASYNTEZ, Russia) (test drug) and Metalyse®, lyophilisate for preparation of solution for intravenous administration 10,000 units (50 mg) (Boehringer Ingelheim International GmbH, Germany) (reference drug) allowed to made following conclusions:

1. Test drug and reference drug *in vitro* increase plasminogen activity in concentration range 0.003 to 0.027 U / ml from 80 - 92% to 188 - 194%, then with increase in concentration of active substance Tenecteplase in model mixtures from 0.082 to 20 U / ml, plasminogen activity decreases to activity values less than 11.25%, i.e. for both drugs, dependence of plasminogen activity on concentration has dome-shaped character with maximum at concentration of 0.027 U / ml.
2. For test drug and reference drug *in vitro*, dependences of change in activity of alpha2-antiplasmin on concentration of active substance have domed appearance with maximum at a concentration of 0.082 U / ml. Dose-dependent increase in activity of alpha2-antiplasmin from 53 - 59% to 300 - 320% was noted for concentration range of 0.003 - 0.082 U / ml. With further increase in concentration of active substance of both drugs, activity of this parameter of fibrinolysis also decreases.
3. During determination of effect of drugs on XIIa-dependent fibrinolysis, it was found that test drug and reference drug dose-dependently reduce time of complete lysis of euglobulin clot in concentration range 0.001 - 0.74 U / ml from 4.6 min to 0.67 min. Increase in drug concentration in model mixtures of more than 0.74 U / ml prevents clot formation.

No differences in biological activity of test drug and reference drug *in vitro* in equivalent concentrations were found for entire range of concentrations selected for testing.

Clinical Studies (Elaxim®)

Study-I

A multicentric, non-comparative clinical trial was conducted to assess the efficacy and tolerability of Elaxim in acute myocardial infarction. All-cause mortality (primary efficacy endpoint) was assessed at 30-days post Elaxim treatment. All patients treated with tenecteplase survived at 30-days, and no mortality was noted. ST-segment resolution > 30% within 90

minutes was observed in 82.97% patients. In patients (n = 26) where coronary angiogram was performed, TIMI 2 or 3 flow was observed in 76.92% patients. This incidence of angiographically confirmed reperfusion correlated well with the ECG ST-segment resolution data. Any bleeding event was observed in 6 patients (12.76%). The bleeding events included 4 events of minor gum bleeds, 1 minor oral bleed and 1 minor event of hematuria.

Study-II

A comparative clinical efficacy and safety study of Elaxim and Metalyse® (Boehringer Ingelheim International GmbH, Germany) was conducted in patients with symptoms of acute myocardial infarction in Republic of Belarus. Patients were administered either Metalyse® (n=10 patients, retrospective control) or Elaxim (n=10 patients) as a single intravenous bolus within 6 hours from the onset of symptoms. The thrombolytic efficacy achieved post Elaxim administration was comparable to Metalyse and no statistically significant differences were observed between the two drugs. TIMI blood flow grade 2 or 3 was achieved in 70% patients in both study arms. The safety and tolerability profile of Elaxim was comparable to Metalyse®.

Study III

The safety and fibrinolytic activity of test product tenecteplase (Elaxim) was compared to reference product Metalyse® in a multicentric Phase- I study conducted in patients with ST-segment elevation myocardial infarction (STEMI) in Russian Federation. A total of 30 patients were enrolled and administered single bolus dose of either Elaxim (n=15) or Metalyse (n=15) within 6 hours of symptoms onset. The data indicated that safety profile of Metalyse® and Elaxim in STEMI patients was comparable. Most of the adverse events observed in the study treatment arms were either of mild or moderate category. The fibrinolytic activity was assessed: *(a)* using ST-segment resolution ≥ 50% within 90 minutes; *(b)* coronary angiography based on TIMI criteria; *(c)* troponins I and/or T values as well as MB fraction of creatine phosphokinase (MB CPhK) and *(d)* 30-day mortality/ rehospitalization due to myocardial infarction. The fibrinolytic activity between the two study treatment groups was comparable and no statistically significant difference was observed between them. ST- segment resolution ≥ 50% within 90 minutes was observed in 53.83% patients in the test product arm and in 53.33% patients in the Metalyse arm. A total of 50% patients achieved complete perfusion (TIMI Grade

3 flow) before percutaneous coronary intervention/ coronary artery bypass grafting in both treatment groups.

5.2 Pharmacokinetic Properties

Absorption and distribution

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Following intravenous bolus administration of 30 mg tenecteplase in patients with acute myocardial infarction, the initially estimated tenecteplase plasma concentration was 6.45 ± 3.60 µg/mL (mean ± SD). The distribution phase represents 31% ± 22% to 69% ± 15% (mean ± SD) of the total AUC following the administration of doses ranges from 5 to 50 mg.

Data on tissue distribution were obtained in studies with radioactively labelled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to which extent tenecteplase binds to plasma proteins in humans. The mean residence time (MRT) in the body is approximately 1 h and the mean (± SD) volume of distribution at the steady-state (Vss) ranged from 6.3 ± 2 L to 15 ± 7 L.

Biotransformation

Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life.

Elimination

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half-life is 24 ± 5.5 (mean ±SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

Linearity/Non-Linearity

The dose linearity analysis based on AUC suggested that tenecteplase exhibits non-linear pharmacokinetics in the dose range studied, i.e. 5 to 50 mg.

Renal and hepatic impairment

Because elimination of tenecteplase is through the liver, it is not expected that renal dysfunction will affect its the pharmacokinetics. This is also supported by animal data. However, the effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans has not been specifically investigated. Accordingly, there is no guidance for the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency.

5.3 Preclinical Safety Data

Acute Toxicity Studies:

1) Acute Intravenous Toxicity Study in Sprague Dawley Rats:

Reduced locomotor activity and ataxic gait were observed in animals treated at the dose level of 100 mg/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal intravenous dose in Sprague Dawley rats is greater than 100 mg/kg body weight.

2) Acute Intravenous Toxicity Study in Swiss Albino Mice:

Reduced locomotor activity and ataxic gait were observed in animals treated at the dose level of 100 mg/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal intravenous dose in Swiss Albino mice is greater than 100 mg/kg body weight.

3) Acute Intravenous Toxicity Study in New Zealand White Rabbits:

Reduced locomotor activity was observed in male and female animals from 50 mg/kg dose group during the study period of 14 days. Discoloration at the site of injection was observed in animals treated at the dose levels of 25 mg/kg and 50 mg/kg body weight. Animals treated at the dose level of 12.5 mg/kg did not reveal any signs of intoxication during the study period. All animals treated at different dose levels survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross examination revealed internal bleeding in the abdominal cavity in one male animal from 50 mg/kg dose group. It was concluded that the acute lethal intravenous dose in New Zealand White rabbits is greater than 50 mg/kg body weight.

4) Acute Intramuscular Toxicity Study in Sprague Dawley Rats:

Reduced locomotor activity and ataxic gait were observed in animals treated at the dose level of 100 mg/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the

treatment. It was concluded that the acute lethal intramuscular dose in Sprague Dawley is greater than 100 mg/kg body weight.

5) Acute Intramuscular Toxicity Study in Swiss albino mice:

Reduced locomotor activity and ataxic gait were observed in animals treated at the dose level of 100 mg/kg body weight. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross pathological examination did not reveal any abnormalities attributable to the treatment. It was concluded that the acute lethal intramuscular dose in Swiss Albino mice is greater than 100 mg/kg body weight.

6) Acute Intramuscular toxicity study in New Zealand White rabbits:

No signs of intoxication were observed in animals treated at different dose levels. All animals survived through the study period of 14 days. Body weight gain of male and female treated animals was found to be normal on day 7 and on day 14. Gross examination revealed internal bleeding in the abdominal cavity in two female animals from 50 mg/kg dose group. It was concluded that the acute lethal intramuscular dose in New Zealand White rabbits is greater than 50 mg/kg body weight.

7) Sub-Chronic Intravenous Toxicity Study (7 day) in Sprague Dawley Rats:

The Sub chronic intravenous toxicity study was designed and conducted to determine the toxicity profile of Recombinant Human TNK-t-PA when administered daily for 7 days in Sprague Dawley rats. Recombinant Human TNK-t-PA diluted with water for injection was administered to animals at the dose levels 2.5 mg/kg, 5 mg/kg and 10 mg/kg body weight. Two additional dose levels were added to the study as 0 mg/kg (Rev.) and 10 mg/kg (Rev.), in order to study the reversibility or delayed occurrence of symptoms, if any. The control animals were administered with vehicle only.

8) Sub-Chronic Intravenous Toxicity Study (7 day) in Swiss Albino Mice:

The Sub-Chronic intravenous toxicity study was designed and conducted to determine the toxicity profile of tenecteplase when administered daily for 7 days in Swiss Albino mice. tenecteplase diluted with water for injection was administered to animals at the dose levels 2.5 mg/kg, 5 mg/kg and 10 mg/kg body weight. Two additional dose levels were added to the study as 0 mg/kg (Rev.) and 10 mg/kg (Rev.), in order to study the reversibility or delayed occurrence of symptoms, if any. The control animals were administered with vehicle only.

9) Sub-Chronic Intravenous Toxicity Study in Pregnant Sprague Dawley Rats: The toxicity study was designed and conducted to determine the developmental toxicity profile of Recombinant Human TNK-t-PA when administered intravenously daily from 10 to 12 days of gestation to pregnant Sprague Dawley rats. Recombinant Human TNK-t-PA dissolved in water for injection was administered to rats via intravenous route at the dose level of 0 mg/kg and 5 mg/kg/day body weight. On gestation day 20, all surviving pregnant rats were sacrificed. Total, live and dead foetuses were examined and recorded.

10) Sub-Chronic Intravenous Toxicity Study (7 day) in New Zealand White Rabbits:

The Sub-Chronic intravenous toxicity study was designed and conducted to determine the toxicity profile of TNK-t-PA when administered daily for 7 days to New Zealand White Rabbit. TNK-t-PA diluted with water for injection was administered to rabbits via intravenous route at the dose levels ranging from 0 mg/kg, 2.5 mg/kg, 5mg/kg and 10 mg/kg body weight. The control animals were administered with vehicle only. All the male and female animals from control and all the treated dose groups up to 10 mg/kg survived throughout the dosing period of 7 days. Animals treated at the dose level of 10 mg/kg, exhibited reduced locomotor activity during the dosing period of 7 days. Animals from 2.5 mg/kg and 5 mg/kg dose groups exhibited no signs of intoxication throughout the dosing period of 7 days. Male and female animals from all the treated dose groups exhibited normal body weight gain at the end of the dosing period of 7 days. Food consumption of control and treated animals was found to be comparable throughout the dosing of 7 days. Haematological analysis and Biochemical analysis revealed no abnormalities attributable to the treatment.

Gross pathological examination revealed minimal to massive blood clots in the peritoneal cavity indicative of internal bleeding in all male and female animals from 5 mg/kg and 10 mg/kg dose groups. Histopathological examination revealed marked focal haemorrhagic necrosis with multifocal early degenerative changes in the hepatic parenchyma, intraluminal mild to marked haemorrhages in the distal convoluted tubules of the kidneys and mild focal subserosal haemorrhages in the urinary bladder in one male animal from 10 mg/kg dose group. Based on these findings the no observed effect level (NOEL) of TNK-t-PA, when administered to New Zealand White Rabbits via intravenous route, over a period of 7 days was found to be 2.5 mg/kg in male and female animals.

11) Comparative repeated dose 7-day intravenous toxicity study of Elaxim 40 (TNKt-PA 40 mg injection) sponsor and Metalyse 40 mg (innovator) by daily administration in the rat followed by the 7-day recovery period

The Comparative Repeated Dose 7-day Intravenous Toxicity study followed by a 7-day recovery period was designed and conducted to determine and compare the toxicity profile of Elaxim 40 (TNK-t-PA 40 mg Injection) Sponsor with Metalyse 40 mg (Innovator) when administered daily for 7 days to the Sprague Dawley rats. Elaxim 40 (TNK-t-PA 40 mg Injection) Sponsor and Metalyse 40 mg (Innovator) was administered to animals at the dose levels of 2.5 mg/kg, 5 mg/kg and 10 mg/kg body weight. Two additional dose levels were added to the study for each of the test item as 0 mg/kg (Rev.) and 10 mg/kg (Rev.), Based on these findings, it can be concluded that the comparative toxicity study in Sprague Dawley rats via intravenous route, over a period of 7 days of Elaxim 40 (TNK-t-PA 40 mg Injection) Sponsor and Metalyse 40 mg (Innovator) supplied by Gennova Biopharmaceuticals Limited, Pune, revealed no significant difference in the toxicological profile of the two substances. The No Observed Adverse Effect Level (NOAEL) for both the substances was found to be 10 mg/kg body weight in male and female animals.

12) Comparative toxicokinetics and immunogenicity study of tenecteplase and Metalyse®

A comparative toxicokinetics and immunogenicity study, designed to compare tenecteplase (test drug, Elaxim) with Metalyse® (reference drug) was performed in Russian Federation. Both test and reference drugs were administered intravenously as single doses in rabbits. The toxicokinetic parameters (AUC0-8, AUC0-∞, MRT, T1/2, C_{max}, T_{max} and Cl) noted post drug administration at doses 100 and 200 U / kg in rabbits did not show statistically significant difference. The immune responses observed between the test and reference group were also similar. These data indicate that toxicokinetics and immunogenicity profile of tenecteplase (Elaxim) was comparable to Metalyse (reference product).

6 Pharmaceutical Particulars

6.1 List of excipients

Arginine

Phosphoric Acid

Polysorbate 20

6.2 Incompatibilities

Precipitation may occur when Tenecteplase is administered in an IV line containing dextrose. Dextrose-containing lines should be flushed with a saline-containing solution prior to and following single bolus administration of Tenecteplase.

6.3 Shelf life

The shelf life is 24 months when lyophilized Tenecteplase Injection is stored at 2 to 8°C. If the reconstituted Tenecteplase is not used immediately, refrigerate the Tenecteplase vial at 2 to 8°C (36–46°F) and use within 8 hours.

6.4 Special precautions for storage

Store lyophilized Tenecteplase at 2 to 8°C. Do not use beyond the expiration date stamped on the vial. If the reconstituted Tenecteplase is not used immediately, refrigerate the Tenecteplase vial at 2 to 8°C (36–46°F) and use within 8 hours.

6.5 Nature and contents of container

- 20 ml glass vial type I, with a grey bromobutyl rubber stopper and a flip-off cap filled with powder for solution for injection.
- 10 ml sterile plastic syringe
- 10 ml Sterile Water for injections for reconstitution in a separate vial
- Sterile needle for single use

6.6 Special precautions for disposal and other handling

Treatment with Tenecteplase should be initiated as soon as possible after onset of symptoms. Aseptically withdraw 10 mL of Sterile Water for Injection (SWFI) from the supplied diluent. Inject the entire contents of the syringe (10 mL) into the Tenecteplase vial containing 50 mg directing the diluent stream into the powder. Slight foaming upon reconstitution is not unusual; any large bubbles will dissipate if the product is allowed to stand undisturbed for several minutes. Gently swirl until contents are completely dissolved. DO NOT SHAKE. The reconstituted preparation results in a colorless to pale yellow transparent solution containing Tenecteplase. Determine the appropriate dose of Tenecteplase and withdraw this volume (in milliliters) from the reconstituted vial with the syringe. Any unused solution should be discarded.

7 Marketing Authorization Holder

Gennova Biopharmaceuticals Limited

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8 Marketing Authorization Numbers

MF-6789/06

9 Date of first authorization/renewal of the authorization

07 August 2006, Amendment dated: 18 May 2007

10 Date of revision of the text

Not Applicable