METALYSE®
(Tenecteplase)

NAME OF THE DRUG

METALYSE® (tenecteplase)

DESCRIPTION

Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology, using an established mammalian cell line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human tPA: a substitution of threonine 103 with asparagine, and a substitution of asparagine 117 with glutamine, both within the kringle 1 domain, and a tetra-alanine substitution at amino acids 296–299 in the protease domain. Cell culture is carried out in nutrient medium containing the antibiotic gentamicin (65 mg/L). However, the presence of the antibiotic is not detectable in the final product (limit of detection is 0.67 µg/vial).

METALYSE® is a sterile, white to off-white, lyophilised powder for single intravenous bolus administration after reconstitution with sterile Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Tenecteplase is a recombinant plasminogen activator that is derived from native tPA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and 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 compared to native tPA.

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 IU, 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.

Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an acute myocardial infarction (AMI) on a dose related basis. A study (TIMI 10B) comparing dose effect of tenecteplase showed that 54% of subjects in the tenecteplase 30 mg dose group achieved a TIMI grade 3 flow, compared with 63% and 66% for the tenecteplase 40 mg and 50 mg dose groups, respectively. These differences were not statistically significant.

Pharmacokinetics

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from the 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 tPA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labelled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver.

Extensive pharmacokinetic characterisation of tenecteplase was performed during Phase I and Phase II clinical trials. After single intravenous bolus injection of tenecteplase in patients with AMI, 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 was 24 ± 5.5 (mean +/- SD) min, which was 5 times longer than native tPA. The terminal half-life was 129 ± 87 min, and plasma clearance was 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. In general, women exhibit lower clearance than men, but this may be explained by the lower body weight of women.

As the kidneys do not appear to be involved in the elimination of tenecteplase, it is not expected that renal dysfunction will affect the pharmacokinetics. The effect of hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known.

CLINICAL TRIALS

A large scale mortality trial (**ASSENT-2**) in approximately 17,000 patients was conducted to compare tenecteplase and alteplase. This was a multicentre, multinational, double-blind, double-dummy, randomised comparison of single bolus body-weight adjusted tenecteplase with an accelerated infusion of body-weight adapted alteplase in patients presenting with AMI.

Adjunctive aspirin and heparin use were directed by the ASSENT-2 protocol as follows:

- Aspirin: 150–325 mg administered as soon as possible, followed by 150–325 mg daily.
- Heparin intravenous (IV): administered as soon as possible: for patients weighing ≤ 67 kg, heparin was administered as a 4,000 units IV bolus followed by infusion at 800 units per hour; for patients weighing > 67 kg, heparin was administered as a 5,000 units IV bolus followed by infusion at 1,000 units per hour. Heparin was continued for 48 to 72 hours with infusion adjusted to maintain aPTT at 50–75 seconds.

The primary objective was to demonstrate therapeutic equivalence for 30-day mortality. Secondary endpoints included net clinical benefit defined as absence of mortality or non-fatal stroke at 30 days, rates of myocardial re-infarction or pulmonary oedema/cardiogenic shock, and rates of invasive cardiac procedures. Safety endpoints included rates of stroke, intracranial haemorrhage (ICH), major bleeding other than ICH and other serious and non-serious adverse events.

Eligibility criteria included onset of chest pain within 6 hours of randomisation and ST-segment elevation or left bundle branch block on electrocardiogram (ECG). Patients were to be excluded from the trial if they received GP IIb/IIIa inhibitors within the previous 12 hours.

The results of the primary endpoints along with other selected endpoints are shown in Table 1.

Table 1: Results from ASSENT-2 study -
Mortality, Stroke, and Combined Outcome of Death or Stroke Measured at Thirty Days

30-day Events	**METALYSE® (n=8,461)**	**Accelerated ACTILYSE® (n=8,488)**	**Relative Risk METALYSE®/ ACTILYSE® (95% CI)**
Mortality	6.2%	6.2%	1.00 (0.89, 1.12)
Intracranial Haemorrhage (ICH)	0.9%	0.9%	0.99 (0.73,1.35)
Any Stroke	1.8%	1.7%	1.07 (0.86, 1.35)
Death or Non-fatal Stroke	7.1%	7.0%	1.01 (0.91, 1.13)

Rates of mortality and the combined endpoint of death or stroke among pre-specified subgroups, including age, gender, time to treatment, infarct location, and history of previous myocardial

infarction, demonstrate consistent relative risks across these subgroups. There was insufficient enrollment of non-Caucasian patients to draw any conclusions regarding relative efficacy in racial subsets.

Rates of in-hospital procedures, including percutaneous transluminal coronary angioplasty (PTCA), stent placement, intra-aortic balloon pump (IABP) use, and coronary artery bypass graft (CABG) surgery, were similar between the tenecteplase and alteplase groups.

The results demonstrated that tenecteplase is therapeutically equivalent to alteplase in reducing 30-day mortality (6.2% for both treatments, at 30 days).

Tenecteplase was also shown to be safe in well-known high-risk populations (older age, lighter weight, and females). Tenecteplase was associated with a significantly lower incidence of major bleeding, fewer coronary artery bypass grafts and improved Killip Class at hospital discharge.

The use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% versus 28.9%, p=0.0003).

This translates into a significantly lower need for transfusions (4.3% versus 5.5%, p=0.0002), reflecting reduced severity of bleeding in the tenecteplase group. ICH occurred at a rate of 0.93% versus 0.94% for tenecteplase and alteplase, respectively.

In the clinical development of tenecteplase, 767 patients were treated with tenecteplase between 6 and 12 hours from symptom onset (6.2% of total number of tenecteplase-treated patients). Numerical differences in favour of tenecteplase over alteplase were observed with regard to 30-day mortality, stroke and ICH. The data indicate that patients can be treated up to 12 hours from symptom onset.

The **ASSENT-4 PCI** study was designed to show if, in 4,000 patients with large myocardial infarctions, pre-treatment with full-dose tenecteplase and concomitant single bolus of up to 4,000 IU unfractionated heparin administered prior to primary Percutaneous Coronary Intervention (PCI) to be performed within 60 to 180 minutes, leads to better outcomes than primary PCI alone. The trial was prematurely terminated with 1,667 randomised patients due to a numerically higher mortality in the facilitated PCI group receiving tenecteplase. The occurrence of the primary endpoint, a composite of death or cardiogenic shock or congestive heart failure within 90 days, was significantly higher in the group receiving the exploratory regimen of tenecteplase followed by routine immediate PCI: 18.6% (151/810) compared to 13.4% (110/819) in the PCI only group, p=0.0045. This significant difference between the groups for the primary endpoint at 90 days was already present in-hospital and at 30 days. Numerically, all of the components of the clinical composite endpoint were in favour of the PCI only regimen: death: 6.7% versus 4.9%, p=0.14; cardiogenic shock: 6.3% versus 4.8%, p=0.19; congestive heart failure: 12.0% versus 9.2%, p=0.06, respectively. The secondary endpoints of re-infarction and repeat target vessel revascularisation were significantly increased in the group pre-treated with tenecteplase: re-infarction: 6.1% versus 3.7%, p=0.0279; repeat target vessel revascularisation: 6.6% versus 3.4%, p=0.0041.

The following adverse events occurred more frequently with tenecteplase prior to PCI: intracranial haemorrhage: 1% versus 0%, p=0.0037; stroke: 1.8% versus 0%, p<0.0001; major bleeds: 5.6% versus 4.4%, p=0.3118; minor bleeds: 25.3% versus 19.0%, p=0.0021; blood transfusions: 6.2% versus 4.2%, p=0.0873; abrupt vessel closure: 1.9% versus 0.1%, p=0.0001.

INDICATIONS

METALYSE® is indicated for the thrombolytic treatment of the acute phase of myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of symptoms. Treatment can be initiated within 12 hours of symptom onset.

CONTRAINDICATIONS

METALYSE® is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding (see also PRECAUTIONS - Bleeding):

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)

- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension i.e. systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 110 mm Hg
- 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 or traumatic cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Active peptic ulceration, during the last 3 months
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months
- Patients receiving other intravenous thrombolytic agents
- Acute pericarditis
- Subacute bacterial endocarditis
- Acute pancreatitis
- Recent (within 10 days) gastrointestinal or genitourinary bleeding
- Recent (within 10 days) obstetrical delivery, organ biopsy, puncture of non-compressible blood vessel (e.g. subclavian or jugular vein puncture)
- Haemostatic defects including those secondary to severe hepatic or renal disease; special attention should be paid to coagulation parameters in patients with significant liver dysfunction

METALYSE® is not for use in patients with a known hypersensitivity to the active substance, tenecteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients.

PRECAUTIONS

The decision to treat a patient with acute myocardial infarction with METALYSE® should be taken under the consultation of a physician experienced in the use of thrombolytic treatment and with the facilities to monitor its use. As with other thrombolytics, it is recommended that when METALYSE® is administered standard resuscitation equipment and medication be available in all circumstances.

Primary Percutaneous Coronary Intervention (PCI)

If primary PCI is scheduled according to the current relevant treatment guidelines, METALYSE® as administered in the ASSENT-4 PCI study (see CLINICAL TRIALS) should not be given.

Bleeding

The most common complication encountered during METALYSE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention.

Should serious bleeding (not controlled by local pressure) occur, any concomitant heparin or antiplatelet agents should be discontinued immediately.

In clinical studies of METALYSE®, patients were treated with both aspirin and heparin. Heparin may contribute to the bleeding risks associated with METALYSE®. The safety of the use of METALYSE® with other antiplatelet agents has not been adequately studied (see PRECAUTIONS: Interactions with other drugs). The use of rigid catheters, intramuscular

injections and non-essential handling of the patient should be avoided for the first few hours following treatment with METALYSE®. Venipunctures should be performed and monitored carefully.

Should an arterial puncture be necessary during the first few hours following METALYSE® therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with METALYSE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of METALYSE® therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels
- Cerebrovascular disease
- Any known or suspected history of ischaemic stroke or transient ischaemic attack more than 6 months previously (see CONTRAINDICATIONS)
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Any known recent (within the past 2 days) intramuscular injection
- Hypertension: systolic BP > 160 mm Hg and/or diastolic BP $\geq$ 110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Acute pancreatitis
- Haemostatic defects, including those secondary to severe hepatic or renal disease
- Severe hepatic dysfunction
- Pregnancy
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age
- Low body weight < 60 kg
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Recent administration of GP IIb/IIIa inhibitors
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

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. During clinical trials with METALYSE®, low fibrinogen consumption and less than 25% reduction in plasminogen was detected at the maximum dose of 50 mg (10,000 IU). Therefore, in case of severe bleeding, substitution of coagulation factors (plasma, platelets) may not be necessary. In 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 should also be considered.

Arrhythmias

Coronary thrombolysis may result in arrhythmia associated with reperfusion.

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

Cholesterol Embolisation

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also

associated with invasive vascular procedures (e.g. cardiac catheterisation, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Cardiac events

Patients with AMI, independent of the treatment given, can experience disease-related events such as cardiogenic shock, pulmonary oedema, heart failure, cardiac arrest, recurrent ischaemia, re-infarction, myocardial rupture, pericarditis, pericardial effusion, cardiac tamponade, mitral regurgitation, venous thrombosis, and electromechanic dissociation.

Thrombo-embolism

The use of METALYSE can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g., mitral stenosis or atrial fibrillation.

Hypersensitivity

No antibody formation to the tenecteplase molecule has been observed after treatment. However, there is no experience with re-administration of METALYSE®. Anaphylactoid reactions associated with the administration of METALYSE® are rare and can be caused by hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. If an anaphylactoid reaction occurs, the injection should be discontinued and appropriate treatment should be initiated.

Effects on fertility

Studies of tenecteplase in animals have not been performed to assess the effects on fertility.

Use in Pregnancy (Category C)

Thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss.

Treatment of rabbits with tenecteplase 0.5-5 mg/kg/day during mid gestation caused vaginal haemorrhage and subsequent embryonic death (approximately 0.8 times maximum clinical exposure, based on AUC). A no effect dose was not established. No fetal abnormalities were detected. There were no adverse effects on the pregnant animal or fetus when tenecteplase was given at doses up to 5 mg/kg daily during early gestation or as a single dose during mid gestation (approximately 8 times maximum clinical exposure, based on AUC).

Studies in animals have not been done to assess the effects of tenecteplase on general reproductive capacity or on offspring development after exposure *in utero*.

There are no adequate or well controlled studies in pregnant women. Tenecteplase should be given to pregnant women only if the potential benefits justify the potential risk to the fetus.

Use in Lactation

It is not known if tenecteplase is excreted into breast milk. Because many drugs are excreted into human milk, caution should be exercised when tenecteplase is administered to breastfeeding women. Studies in animals have not been done to assess the effect of tenecteplase on neonatal development.

Paediatric Use

Safety and efficacy in children has not been established. Therefore treatment of such patients is not recommended.

Use in the elderly

The risks of therapy may be increased in the elderly.

Carcinogenicity

Studies of tenecteplase in animals have not been performed to assess the carcinogenic potential.

Genotoxicity

Studies of tenecteplase in animals have not been performed to assess its mutagenicity.

Interactions with Other Medicines

No formal interaction studies with METALYSE® and agents 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 agents commonly used in patients with AMI and concomitantly used with METALYSE®.

Agents that affect coagulation or those that alter platelet function (example low molecular weight heparin) may increase the risk of bleeding prior to, during or after METALYSE® therapy. The concomitant use of GP IIb/IIIa antagonists increases the risk of bleeding.

Current data generally do not support the use of thrombolytic therapy in patients when the ECG shows only ST depression (with the exception of those patients with a "true posterior" infarct, as indicated by tall R waves and marked ST depression in leads V_1 - V_3).

ADVERSE EFFECTS

Haemorrhage: The most frequent adverse event associated with the use of METALYSE® is haemorrhage. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanently disability or death.

The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial bleeding, normally from injection sites.

Neurological symptoms such as somnolence, aphasia, hemiparesis and convulsion may be associated with intracranial haemorrhage.

The frequencies given below are based on corresponding occurrences in a clinical trial involving 8,258 patients treated with METALYSE for myocardial infarction.

The bleeding events reported include:

General disorders and administration site conditions:

>10%: superficial bleeding, normally from punctures or damaged blood vessels

Vascular disorders:

>10%: bleeding

Skin and subcutaneous tissue disorders:

>1% and ≤10%: ecchymosis

Renal and urinary disorders:

>1% and ≤10%: urogenital haemorrhage (such as haematuria, haemorrhage urinary tract)

Respiratory, thoracic and mediastinal disorders:

>1% and ≤10%: epistaxis

>0.1% and ≤1%: pulmonary haemorrhage

Gastrointestinal disorders:

>1% and ≤10%: gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage),

>0.1% and ≤1%: retroperitoneal haemorrhage (such as retroperitoneal haematoma)

Nervous system disorders:

>0.1% and ≤1%: intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage)

Cardiac disorders:

>0.01% and ≤0.1%: pericardial haemorrhage

Eye disorders:

>0.1% and ≤1%: eye haemorrhage

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

In the ASSENT-2 study, the following non-ICH bleeding events were reported (Table 2).

Table 2: Results from ASSENT-2 study - Non-ICH Bleeding Events

	METALYSE® (n=8,461)	**Accelerated ACTILYSE® (n=8,488)**	**Relative Risk METALYSE®/ ACTILYSE® (95% CI)**
Major bleeding[a]	4.7%	5.9%	0.78 (0.69, 0.89)
Minor bleeding	21.8%	23.0%	0.94 (0.89, 1.00)
Units of transfused blood Any 1–2 > 2	 4.3% 2.6% 1.7%	 5.5% 3.2% 2.2%	 0.77 (0.67, 0.89)
[a]Major bleeding is defined as bleeding requiring blood transfusion or leading to haemodynamic compromise.			

Non-intracranial major bleeding and the need for blood transfusions were lower in patients treated with METALYSE®.

Types of major bleeding reported in 1% or more of the patients were haematoma (1.7%) and gastrointestinal tract (1%). Types of major bleeding reported in less than 1% of the patients were urinary tract, puncture site (including cardiac catheterisation site), retroperitoneal, respiratory tract, and unspecified. Types of minor bleeding reported in 1% or more of the patients were haematoma (12.3%), urinary tract (3.7%), puncture site (including cardiac catheterisation site) (3.6%), pharyngeal (3.1%), gastrointestinal tract (1.9%), epistaxis (1.5%), and unspecified (1.3%).

The total number of patients who presented with strokes, as classified by the investigator, was 292: 151 patients (1.78%) in the tenecteplase-treated group and 141 patients (1.66%) in the alteplase-treated group. The total number of patients presenting with ICH, was 159: 79 patients (0.93%) in the tenecteplase-treated group and 80 patients (0.94%) in the alteplase-treated group. The differences between treatment groups was not statistically significant (p=0.5552 and p=1.0000, respectively).

The incidence of ICH and total stroke increased with age in both tenecteplase- and alteplase-treated patients. In patients > 75 years of age, the incidence of stroke was 3.15% and 4.39%, respectively, and for ICH was 1.72% and 2.62%, respectively.

Other adverse events reported include:

Cardiac disorders:

>10%: reperfusion arrhythmias (such as asystole, accelerated idioventricular arrhythmia, arrhythmia, extrasystoles, atrial fibrillation, first degree atrioventricular block - complete atrioventricular block, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with METALYSE®. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

Gastrointestinal disorders:

>1% and ≤10%: nausea, vomiting

Investigations:

>10%: blood pressure decreased

>1% and ≤10%: body temperature increased

Vascular disorders:

>0.1% and ≤1%: embolism

Injury, poisoning and procedural complications:

≤0.01%: fat embolism, which may lead to corresponding consequences in the organs concerned

Immune system disorders:

>0.1% and ≤1%: anaphylactoid reactions (including rash, urticaria, bronchospasm, laryngeal oedema)

Surgical and medical procedures:

>1% and ≤10%: transfusion

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

>10%: hypotension, heart rate and rhythm disorders, angina pectoris

>1% and ≤10%: recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema

>0.1% and ≤1%: cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture

>0.01% and ≤0.1%: pulmonary embolism

not known: stent occlusion

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

From the data received after marketing authorisation no additional adverse effects have been detected from spontaneous reporting.

DOSAGE AND ADMINISTRATION

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

Patient's body weight category (kg)	METALYSE® (IU)	METALYSE® (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

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line, which has been used for administration of 0.9% Sodium Chloride solution only, may be used for administration of METALYSE® and the intravenous line should be flushed after METALYSE® injection for proper delivery. METALYSE® is incompatible with glucose solution.

METALYSE® should not be mixed with other medication, neither in the same injection-vial nor the same intravenous line (not even with heparin). Before dilution or administration, parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit.

The reconstituted solution is for single use, in a single patient. Any excess solution should be discarded.

Adjunctive therapy

Antithrombotic adjunctive therapy is recommended according to the current International guidelines for the management of patients with ST-elevation myocardial infarction.

For the antithrombotic adjunctive therapy regimen used in the ASSENT-2 study, see CLINICAL TRIALS.

Reconstitution and handling

METALYSE® should be reconstituted by adding the complete volume of Water for Injections (WFI) from the pre-filled syringe to the vial containing the powder for injection. Reconstitution can be performed using either the vial adapter or the needle provided with METALYSE®. The reconstitution process using the vial adapter is described below (refer to the pictograms inside the carton lid for further information):

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient (see DOSAGE AND ADMINISTRATION).
2. Check that the cap of the vial is still intact.
3. Remove the flip-off cap from the vial.
4. Remove the tip-cap from the pre-filled syringe. Then immediately screw the pre-filled syringe securely onto the vial adapter and use the spike of the vial adapter to penetrate the vial stopper (in the middle).
5. Add the WFI into the vial by pushing the syringe plunger down slowly to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Transfer the appropriate volume of reconstituted solution of METALYSE® into the syringe, based on the patient's weight.
10. Disconnect the syringe from the vial adapter.
11. METALYSE® is to be administered as a single intravenous bolus in about 10 seconds. It should not be administered in a line containing glucose.

12. Any unused solution should be discarded.

The reconstituted solution contains 5 mg (1,000 IU) tenecteplase per mL.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 2-8°C or 8 hours at 30°C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding, substitution therapy may be considered (plasma, platelets) (see also PRECAUTIONS).

PRESENTATION

METALYSE® 40 mg:

1 vial contains 40 mg (8,000 IU) tenecteplase

1 pre-filled syringe contains 8 mL WFI

1 vial adapter and 1 needle (for reconstitution)

METALYSE® 50 mg:

1 vial contains 50 mg (10,000 IU) tenecteplase

1 pre-filled syringe contains 10 mL WFI

1 vial adapter and 1 needle (for reconstitution)

The excipients are L-arginine, phosphoric acid and polysorbate 20.

STORAGE CONDITIONS

Store below 30°C. Before use, keep in the outer carton in order to protect from light.

The potency of METALYSE® expressed in International Units (IU) is based on a reference standard that is specific for tenecteplase. The IU for tenecteplase is not comparable with units used for other thrombolytic agents.

POISON SCHEDULE

Schedule 4

NAME AND ADDRESS OF THE SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 WATERLOO ROAD
NORTH RYDE NSW 2113

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