AUSTRALIAN PRODUCT INFORMATION – METALYSE (tenecteplase) 40 mg and 50 mg powder for injection

1 NAME OF THE MEDICINE

tenecteplase (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

METALYSE 40 mg:
1 vial contains 40 mg (8,000 U) tenecteplase
1 pre-filled syringe containing 8 mL Water for Injections (WFI)
1 vial adapter (for reconstitution)

METALYSE 50 mg:
1 vial contains 50 mg (10,000 U) tenecteplase
1 pre-filled syringe containing 10 mL Water for Injections (WFI)
1 vial adapter (for reconstitution)

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

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

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

METALYSE should be administered on the basis of body weight, with a maximum dose of 50 mg (10,000 U). The volume required to administer the correct dose can be calculated from Table 1 below:

Table 1: Dosing table for acute myocardial infarction (AMI)

Patient's body weight category (kg)	METALYSE (U)	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

Elderly patients (≥ 75 years)

METALYSE should be administered with caution in elderly patients (≥ 75 years) due to a higher bleeding risk (see Sections 5.1 Pharmacodynamic Properties, Clinical Trials and 4.4 Special Warnings and Precautions for Use).

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 Section 5.1 Pharmacodynamic Properties, Clinical Trials.

For coronary intervention refer to Section 4.4 Special Warnings and Precautions for Use.

Method of administration

The reconstituted solution should be administered intravenously and is for immediate use.

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

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

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 a needle. 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 Section 4.2 Dose and Method of 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. Keep the syringe attached to the vial adapter and 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. Unscrew the syringe from the vial adapter.
11. 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. 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.
12. METALYSE is to be administered as a single intravenous bolus in about 10 seconds. It should not be administered in a line containing dextrose as METALYSE is incompatible with dextrose solution.
13. The line should be flushed after METALYSE injection for proper delivery.
14. Any unused solution should be discarded.

4.3 CONTRAINDICATIONS

METALYSE is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding (see also Section 4.4 Special Warnings and Precautions for Use, 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) (please see section 4.4 Special Warnings and Precautions for Use, Bleeding)
- 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The decision to treat a patient with AMI 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.

The appropriate presentation of tenecteplase product should be chosen carefully and in line with the indication. METALYSE 40 mg and 50 mg are intended for use in acute myocardial infarction only.

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

Coronary intervention

Transfer to a coronary intervention capable facility for adjunctive Percutaneous Coronary Intervention (PCI):

Patients receiving METALYSE as primary coronary recanalization treatment should be transferred without delay to a coronary intervention capable facility for angiography and timely coronary intervention within 6-24 hours or earlier if medically indicated (see Section 5.1 Pharmacodynamic Properties, Clinical Trials).

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 Section 5.1 Pharmacodynamic Properties, 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). 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 Section 4.3 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 ≥ 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 (>75 years of age)
- Low body weight < 60 kg
- Patients currently receiving oral anticoagulants, e.g. warfarin sodium – the use of METALYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity

- 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 U). 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 sustained 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.

Use in the elderly

METALYSE should be administered with caution in elderly patients (≥ 75 years) due to a higher bleeding risk (see Sections 5.1 Pharmacodynamic Properties, Clinical Trials and 4.2 Dose and Method of Administration).

Paediatric Use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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 human milk. Because many drugs are excreted into human milk, caution should be exercised when METALYSE is administered to breastfeeding women and a decision must be made whether breast-feeding should be discontinued for the first 24 hours after administration of METALYSE. Studies in animals have not been done to assess the effect of tenecteplase on neonatal development.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

Summary of the safety profile

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, permanent 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 (Table 2) are based on corresponding occurrences in a clinical trial involving 8,258 patients treated with METALYSE for myocardial infarction.

The corresponding frequency category estimation for each adverse drug reaction is based on 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 2: Bleeding events reported in clinical trial patients treated for myocardial infarction

System Organ Class	Very common	Common	Uncommon	Rare
General disorders and administration site conditions	superficial bleeding, normally from punctures or damaged blood vessels			
Vascular disorders	bleeding			
Skin and subcutaneous tissue disorders		ecchymosis		
Renal and urinary disorders		urogenital haemorrhage (such as haematuria, haemorrhage urinary tract)		
Respiratory, thoracic and mediastinal disorders		epistaxis	pulmonary haemorrhage	

System Organ Class	Very common	Common	Uncommon	Rare
Gastrointestinal disorders		gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage)	retroperitoneal haemorrhage (such as retroperitoneal haematoma)	
Nervous system disorders			intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage)	
Cardiac disorders				pericardial haemorrhage
Eye disorders			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 3).

Table 3: 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.

Table 4: Other adverse events classified according to frequency and system organ class

System Organ Class	Very Common	Common	Uncommon	Very rare
Cardiac disorders	reperfusion arrhythmias*			
Gastrointestinal disorders		nausea, vomiting		
Investigations	blood pressure decreased	body temperature increased		
Vascular disorders			embolism	
Injury, poisoning and procedural complications				fat embolism, which may lead to corresponding consequences in the organs concerned
Immune system disorders			anaphylactoid reactions (including rash, urticaria, bronchospasm, laryngeal oedema)	
Surgical and medical procedures		transfusion		

* (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.

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, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema

Uncommon: cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture

Rare: 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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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 Section 4.4 Special Warnings and Precautions for Use).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antithrombotic agents, enzymes

ATC code: B01A D11

Mechanism of action

Tenecteplase is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology, using an established mammalian cell line (Chinese Hamster Ovary cells).

Tenecteplase is a recombinant 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 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 t-PA.

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.

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.

Clinical Trials

<u>ASSENT-2 study</u>

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 5.

Table 5: 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.

ASSENT-4 PCI study

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 U 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.

STREAM study

The STREAM study was designed to evaluate the efficacy and safety of a pharmaco-invasive strategy of early fibrinolytic treatment with tenecteplase and additional antiplatelet and anticoagulant therapy followed by angiography within 6-24 hours or rescue coronary intervention versus a strategy of standard primary PCI. The STREAM study was a proof-of-concept study. All statistical tests were of an exploratory nature, and confidence intervals and p-values are provided for descriptive purposes only.

The study population consisted of patients with ST elevation AMI within 3 hours of onset of symptoms not able to undergo primary PCI within 1 hour of first medical contact.

A sample size of approximately 1000 patients per treatment group was planned for this exploratory study. After 382 patients had been enrolled (19.5% of the planned study population), the dose of the tenecteplase bolus was reduced by half for the patients ≥ 75 years because of a higher incidence of intracranial haemorrhage (ICH) in this sub-group.

1892 patients were randomised by means of an interactive voice response system. The primary endpoint, a composite of death or cardiogenic shock or congestive heart failure or re-infarction within 30 days was observed in 12.4% (116/939) of the pharmaco-invasive arm versus 14.3% (135/943) in the primary PCI arm (relative risk 0.86 (0.68-1.09)). Urgent angiography/Rescue PCI was required in approximately 40% of patients of the pharmaco-invasive arm.

Single components of the primary composite endpoint for the pharmaco-invasive strategy versus primary PCI respectively were observed with the following frequencies (Table 6):

Table 6: Single components of primary composite endpoint for pharmaco-invasive strategy vs primary PCI

	Pharmaco-invasive (n=944)	Primary PCI (n=948)	P
Composite death, shock, congestive heart failure, reinfarction	116/939 (12.4%)	135/943 (14.3%)	0.21
All-cause mortality	43/939 (4.6%)	42/946 (4.4%)	0.88
Cardiogenic shock	41/939 (4.4%)	56/944 (5.9%)	0.13
Congestive heart failure	57/939 (6.1%)	72/943 (7.6%)	0.18
Reinfarction	23/938 (2.5%)	21/944 (2.2%)	0.74
Cardiac mortality	31/939 (3.3%)	32/946 (3.4%)	0.92

The observed incidence of major and of minor non-ICH bleeds were similar in both groups (Table 7):

Table 7: Incidence of major and minor non-ICH bleeds

	Pharmaco-invasive (n=944)	Primary PCI (n=948)	P
Major non-ICH bleed	61/939 (6.5%)	45/944 (4.8%)	0.11
Minor non-ICH bleed	205/939 (21.8%)	191/944 (20.2%)	0.40

Table 8: Incidence of total strokes and intracranial haemorrhage

	Pharmaco-invasive (n=944)	Primary PCI (n=948)	P
Total stroke (all types)	15/939 (1.6%)	5/946 (0.5%)	0.03*
Intracranial haemorrhage	9/939 (0.96%)	2/946 (0.21%)	0.04**
Intracranial haemorrhage after protocol amendment to half dose in patients ≥ 75 years	4/747 (0.5%)	2/758 (0.3%)	0.45

* the incidences in both groups are those expected in STEMI patients treated by fibrinolytics or primary PCI (as observed in previous clinical studies).
** the incidence in the pharmaco-invasive group is as expected for fibrinolysis with METALYSE (as observed in previous clinical studies).

None of the differences between groups displayed in the above tables reached the threshold of statistical significance except for the incidence of total strokes and ICH, however the incidences in the pharmaco-invasive group were as observed in previous clinical studies.

After the dose reduction of tenecteplase by half in patients ≥ 75 years there was no further intracranial hemorrhage (0 of 97 patients) (95% CI: 0.0-3.7) versus 8.1% (3 of 37 patients) (95% CI: 1.7-21.9) prior to the dose reduction. The bounds of the confidence interval of the observed incidences prior and after dose reduction are overlapping.

In patients ≥ 75 years the observed incidence of the primary efficacy composite end point for the pharmaco-invasive strategy and primary PCI were as follows: before dose reduction 11/37 (29.7%)

(95% CI: 15.9-47.0) vs. 10/32 (31.3%) (95% CI: 16.1-50.0), after dose reduction: 25/97 (25.8%) (95% CI: 17.4-35.7) vs. 25/88 (24.8%) (95% CI: 19.3-39.0). In both groups the bounds of the confidence interval of the observed incidences prior and post dose reduction are overlapping.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Following i.v. bolus administration of 30 mg tenecteplase in patients with AMI, 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. 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. A total of 113 AMI patients were enrolled and blood sampling for pharmacokinetics was conducted in 82 patients (72 male and 10 female).

Data on tissue distribution were obtained in studies with radioactively labelled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver.

Metabolism

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 t-PA, resulting in a prolonged half-life.

Excretion

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 t-PA. 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.

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.

Special populations

Renal and hepatic impairment

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are arginine, phosphoric acid and polysorbate 20.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

The reconstituted solution has been demonstrated to be stable for 24 hours at 2-8°C or for 6 hours at room temperature.

To reduce microbiological hazard, the product should be used immediately after reconstitution. If storage of the reconstituted solution is necessary, it should be held at 2-8°C for not more than 24 hours and is the responsibility of the user.

6.5 NATURE AND CONTENTS OF CONTAINER

METALYSE 40 mg: 1 glass vial containing 40 mg (8,000 U) tenecteplase, 1 pre-filled syringe containing 8 mL WFI and 1 vial adapter (for reconstitution).

METALYSE 50 mg: 1 glass vial containing 50 mg (10,000 U) tenecteplase, 1 pre-filled syringe containing 10 mL WFI and 1 vial adapter (for reconstitution).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human t-PA: 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).

CAS Number

191588-94-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
78 Waterloo Road
North Ryde NSW 2113

www.boehringer-ingelheim.com.au

9 DATE OF FIRST APPROVAL

9 November 2000

10 DATE OF REVISION

15 July 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Title	Inclusion of strengths next to the Tradename
4.2, 4.8	Editorial changes
4.4	Inclusion of a precaution to ensure the correct METALYSE presentation is chosen carefully and in line with the indication
6.4	Editorial update to in-use storage statement
6.5	Editorial update to include ‘glass’