

NEW ZEALAND DATASHEET

1. PRODUCT NAME

METALYSE 40 mg powder and solvent for solution for injection
METALYSE 50 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METALYSE 40 mg:

1 vial containing 8,000 units (40 mg) tenecteplase. 1 prefilled syringe containing 8 mL water for injection.

(Not marketed)

METALYSE 50 mg:

1 vial contains 10,000 units (50 mg) tenecteplase.
1 prefilled syringe containing 10 mL water for injection.

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

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a fibrin-specific plasminogen activator produced in a Chinese hamster ovary cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white powder and solvent for solution for injection. Reconstitution results in a colourless to pale yellow, transparent, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 symptom onset. Treatment can be initiated within 12 hours of symptom onset.

4.2 Dose and method of administration

METALYSE should be administered as early as possible after symptom onset 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)	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

Adjunctive Therapy

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

For coronary intervention see section 4.4.

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 5 to 10 seconds.

4.3 Contraindications

METALYSE is contraindicated in:

- Patients with known hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients
- Situations associated with a risk of bleeding such as:
 - Significant bleeding disorder either at present or within the past 6 months, known haemorrhagic diathesis
 - Patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (INR > 1.3) (see section 4.4, subsection “Bleeding”)
 - Any history of central nervous damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
 - Severe uncontrolled arterial hypertension
 - Major surgery, biopsy of 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
 - Arterial aneurysm and known arterial/venous malformation
 - Neoplasm with increased bleeding risk
 - Acute pericarditis and/or subacute bacterial endocarditis
 - Acute pancreatitis
 - Haemorrhagic stroke or stroke of unknown origin at any time
 - Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months.

4.4 Special warnings and precautions for use

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 that use. This does not preclude the pre-hospital use of METALYSE. As with other thrombolytics, it is recommended that when METALYSE is administered, standard resuscitation equipment and medication be available in all circumstances.

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).

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) should not be given.

Bleeding

Although METALYSE is characterised by a significantly lower incidence of extracranial bleeding as compared to ACTILYSE[®], bleeding can occur. The most common complication encountered during METALYSE therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during METALYSE therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including those following catheter insertion, arterial and venous puncture, cutdown and needle puncture). The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with METALYSE.

Should serious bleeding occur, in particular cerebral haemorrhage, any 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 should also be considered.

The use of METALYSE therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg (see also Section 4.3)
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleedings (within the past 10 days)
- 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 treatment: The use of METALYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.

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.

Glyco-Protein IIb/IIIa antagonists

The concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

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.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies with METALYSE 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 METALYSE.

Drugs affecting coagulation/platelet function

Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after METALYSE therapy (see Section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

There is a limited amount of data from the use of METALYSE in pregnant women.

Nonclinical studies performed with tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the drug 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 (see section 5.3).

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

Breastfeeding

It is not known if tenecteplase is excreted into breast milk. Caution should be exercised when METALYSE is administered to a nursing woman and a decision must be made whether breastfeeding should be discontinued for the first 24 hours after administration of METALYSE.

Fertility

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

a. Summary of the safety profile

As with other thrombolytic agents, haemorrhage is the most common adverse reaction associated with the use of METALYSE. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.

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

- superficial bleeding, normally from injection sites
- internal bleeding at any site or body cavity.

With intracranial haemorrhage neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion may be associated.

b. 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

System Organ Class	Adverse reaction	Frequency
Immune system disorders	anaphylactoid reaction including - rash - urticaria - bronchospasm - laryngeal oedema	Rare
Nervous system disorders	intracranial haemorrhage such as - cerebral haemorrhage - cerebral haematoma - haemorrhagic stroke - haemorrhagic transformation stroke - intracranial haematoma - subarachnoid haemorrhage	Uncommon
Eye disorders	eye haemorrhage	Uncommon
Cardiac disorders	reperfusion arrhythmia such as - asystole - accelerated idioventricular arrhythmia - arrhythmia - extrasystoles - atrial fibrillation - atrioventricular block first degree - atrioventricular block complete - bradycardia - tachycardia - ventricular arrhythmia - ventricular fibrillation - ventricular tachycardia occur in close temporal relationship to treatment with METALYSE.	Uncommon
	pericardial haemorrhage	Rare
Vascular disorders	haemorrhage	Very common
	embolism	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Common
	pulmonary haemorrhage	Rare
Gastrointestinal disorders	gastrointestinal haemorrhage such as - gastric haemorrhage - gastric ulcer haemorrhage - rectal haemorrhage - haematemesis - melaena - mouth haemorrhage	Common
	nausea	Not known
	vomiting	Not known
	retroperitoneal haemorrhage such as - retroperitoneal haematoma	Uncommon
Skin and subcutaneous tissue disorders	ecchymosis	Common
Renal and urinary disorders	urogenital haemorrhage such as - haematuria - haemorrhage urinary tract	Common
General disorders and administration site conditions	injection site haemorrhage, puncture site haemorrhage	Common
Investigations	blood pressure decreased	Rare
	body temperature increased	Not known

Injury, poisoning and procedural complications	fat embolism, which may lead to corresponding consequences in the organs concerned	Not known
Surgical and medical procedures	transfusion	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

METALYSE pharmacotherapeutic group is Antithrombotic agent, ATC code: B01AD11.

Mechanism of action

The active ingredient of METALYSE (tenecteplase) is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modification 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 α 2-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 a 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.

Clinical efficacy and safety

Patency rates 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 acute myocardial infarction (AMI) on a dose related basis.

ASSENT 2 study

A large scale mortality trial (ASSENT 2) in approximately 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments at 30 days) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs 28.9%, $p = 0.0003$). The reduction of the risk of bleeding is likely to be related to the increased fibrin specificity of tenecteplase and to its weight adapted regimen.

This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, $P = 0.0002$). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively. In

the 475 patients treated beyond 6 hours numerical differences in favour of tenecteplase were observed with regard to 30-day mortality (4.3% vs. 9.6%), stroke (0.4% vs. 3.3%) and ICH (0% vs. 1.7%).

ASSENT 3 study

The ASSENT 3 study aimed to optimise tenecteplase concomitant antithrombotic therapy towards both improving early patency rates and maintaining perfusion, mainly to overcome the paradoxical pro-coagulant effect arising from the release by clot lysis of trapped thrombin. Three different concomitant antithrombotic regimens were compared in 6,095 patients:

Full-dose tenecteplase + unfractionated heparin (UFH) versus full-dose tenecteplase + low molecular weight (LMW) heparin (enoxaparin) versus half-dose tenecteplase + unfractionated heparin + full dose abciximab.

UFH was used as recommended by AHA/ACC guidelines according to a full body-weight adapted low dose regimen as follows: A single IV bolus of 60 IU/kg (maximum 4000 IU) immediately followed by an intravenous infusion of 12 IU/kg/hr (maximum 1000 IU/hr) for the first 3 hours, thereafter according to aPTT monitoring for up to 48 hours to maintain aPTT at 50-70 seconds. 30-day mortality rates are respectively 6.0%, 5.4% and 6.6%, the in-hospital major bleeds (other than ICH) 2.16%, 3.04% and 4.32% and the intracranial haemorrhage 0.93%, 0.88% and 0.94%. The recommended ACC/AHA fully body-weight adjusted low dose unfractionated heparin regimen used in ASSENT 3 concomitantly with tenecteplase results in less systemic bleeding but similar ICH rates compared to the more aggressive unfractionated heparin regimen dosing used in ASSENT 2 without loss of efficacy.

ASSENT 3 PLUS study

ASSENT 3 PLUS, a satellite study of ASSENT 3, was designed to investigate the pre-hospital setting. The efficacy and safety of full-dose tenecteplase + unfractionated heparin versus full-dose tenecteplase + low molecular weight (LMW) heparin (enoxaparin) has been evaluated in 1639 patients. The study design and treatments dosage used are identical to those of the ASSENT 3 study. Pre-hospital reperfusion therapy with tenecteplase and UFH or enoxaparin allowed treatment within 2 hours of symptom onset in >50% of the patients with STEMI.

From ASSENT 3 and 3 PLUS studies, pre-hospital as well as in-hospital adjunctive therapy with enoxaparin reduced the incidence of ischemic complications as compared to adjunctive therapy with UFH: the incidence of 30-day efficacy composite endpoint (death, re-infarction, refractory ischaemia) was respectively 11.4% versus 15.4% in ASSENT 3 and 14.2% versus 17.4% in ASSENT 3 PLUS. However, in the pre-hospital setting, tenecteplase with enoxaparin at the dose used was associated with an increased risk of major bleeding and ICH in patients >75 years of age.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

ASSENT-4 PCI study

The ASSENT-4 PCI study was designed to show if in 4000 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 1667 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 re-infarction and repeat target vessel revascularisation were significantly increased in the group pre-

treated with tenecteplase: reinfarction: 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 study population consisted of patients with ST elevation acute myocardial infarction within 3 hours of onset of symptoms not able to undergo primary PCI within one 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 \geq 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)).

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

	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:

	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

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 acute myocardial infarction, the initially estimated tenecteplase plasma concentration was $6.45 \pm 3.60 \mu\text{g/mL}$ (mean \pm SD). The distribution phase represents $31\% \pm 22\%$ to $69\% \pm 15\%$ (mean \pm SD) of the total AUC following the administration of doses ranges from 5 to 50 mg. 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. 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 (\pm SD) volume of distribution at the steady-state (V_{ss}) ranged from $6.3 \pm 2 \text{ L}$ to $15 \pm 7 \text{ L}$.

Biotransformation

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.

Elimination

After single intravenous bolus injection of tenecteplase in patients with AMI, tenecteplase antigen exhibits biphasic elimination from the plasma. There is no dose dependent clearance of tenecteplase, in the therapeutic dose range. The initial, dominant half-life was 24 ± 5.5 (mean \pm 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 moderate increase in tenecteplase clearance, and increasing age resulted in a slight decrease in clearance. Women exhibit a 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.

Special populations

Renal and hepatic impairment

Because elimination of tenecteplase is through the liver, it is not expected that renal dysfunction will affect the pharmacokinetics of METALYSE. 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.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by transient changes of ECG but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was confined to the rabbit, as a sensitive species. Tenecteplase induced no teratogenicity. Repeated dose administration resulted in bleeding with secondary mortality of dams. In a few cases abortion and resorption of the foetus occurred. Effects were not seen after single dose administration of tenecteplase.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine

phosphoric acid

polysorbate 20

Metalysse may contain a trace residue of gentamicin from the manufacturing process

Diluent:

water for injection

6.2 Incompatibilities

METALYSE is incompatible with dextrose infusion solutions. No other medicinal product should be added to the injection solution or infusion line.

6.3 Shelf life

Shelf life as packaged for sale

36 months

Reconstituted solution

The reconstituted solution has been demonstrated to be stable for 24 hours at 2-8°C and for 8 hours at 30°C. From a microbial 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 to 8°C or 8 hours at 30°C.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

METALYSE 40 mg (8,000U) and 1 prefilled syringe with 8 mL water for injection. (Not marketed)

METALYSE 50 mg (10,000U) and 1 prefilled syringe with 10 mL water for injection.

6.6 Special precautions for disposal and other handling

Instructions for use and handling, and disposal

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.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient (see section 4.2).
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 syringe. Then immediately screw the pre-filled syringe on the vial adapter and penetrate the vial stopper in the middle with the spike of the vial adapter.
5. Add the water for injections 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, transparent solution. Only clear solution without particles should be used.
8. Directly before the solution is 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 drugs, neither in the same infusion-vial nor the same venous line (not even with heparin).
12. METALYSE should be administered to the patient, intravenously over 5 to 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.
15. Alternatively, the reconstitution can be performed with a needle instead of the included vial adapter.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
 P O Box 76-216
 Manukau City
 Auckland
 NEW ZEALAND

Telephone: 0800 802 461

9. DATE OF FIRST APPROVAL

17 May 2001

10. DATE OF REVISION OF THE TEXT

14 September 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2, 6.6	Revision of dosage and administration wording, editorial changes
4.4	Inclusion of traceability statement, editorial changes
4.6	Strengthening of lactation precaution
4.8, 6.4	Editorial changes
6.3	Shelf-life revised from 24 months to 36 months
6.6	Removal of reference to single-use needle
8	Deletion of facsimile number