NEW ZEALAND DATA SHEET

1. PRODUCT NAME

METALYSE 25 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METALYSE 25 mg:
1 vial contains 5,000 units (25 mg) tenecteplase.

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

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 in adults for the thrombolytic treatment of acute ischaemic stroke (AIS) within 4.5 hours from last known well and after exclusion of intracranial haemorrhage.

4.2 Dose and method of administration

METALYSE should be administered as early as possible and no later than 4.5 hours after last known well and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent; therefore, earlier treatment increases the probability of a favourable outcome.

METALYSE should be administered on the basis of body weight, with a maximum single dose of 5,000 U (25 mg) tenecteplase.

The volume required to administer the correct total dose can be calculated from Table 1 below:

Table 1: Dosing table for acute ischaemic stroke (AIS)

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (mL)
< 60	3,000	15.0	3.0
≥ 60 to < 70	3,500	17.5	3.5
≥ 70 to < 80	4,000	20.0	4.0
≥ 80 to < 90	4,500	22.5	4.5

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (mL)
≥ 90	5,000	25.0	5.0

Adjunctive therapy

Drugs affecting coagulation/platelet function
The safety and efficacy of this regimen with concomitant treatment with heparin or platelet aggregation inhibitors such as aspirin during the first 24 hours after treatment with METALYSE have not been investigated sufficiently. Therefore, administration of intravenous heparin or platelet aggregation inhibitors such as aspirin should be avoided in the first 24 hours after treatment with METALYSE due to an increased haemorrhagic risk.

If heparin is required for other indications the dose should not exceed 10,000 IU per day, administered subcutaneously.

Thrombectomy
Patients eligible for intravenous tenecteplase should receive intravenous tenecteplase even if mechanical thrombectomy is being considered.

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.

For instructions on reconstitution of the medicine before administration, see Section 6.6.

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 listed in Section 6.1
- Situations associated with a risk of bleeding such as:
  - Significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
  - Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
  - Severe uncontrolled arterial hypertension (see Section 4.4, subsection "Blood pressure monitoring")
  - Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
  - Active ulcerative gastro-intestinal disease
  - Known arterial aneurysm and/or arterial/venous malformation
  - Neoplasm with increased bleeding risk
  - Bacterial endocarditis, pericarditis
  - Acute pancreatitis
  - Acute ischaemic stroke without disabling neurological deficit
  - History or evidence or suspicion of intracranial haemorrhage including subarachnoid haemorrhage
  - Patients receiving effective anticoagulation (e.g. vitamin K antagonists with INR > 1.7) (see Section 4.4, subsection "Bleeding")

4.4 Special warnings and precautions for use

The appropriate presentation of tenecteplase product should be chosen carefully and in line with the indication. METALYSE 25 mg is intended for use in acute ischaemic stroke only.

METALYSE should be prescribed by physicians 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.

Treatment must be performed under the responsibility of physicians trained and experienced in neurovascular care. For the indication verification, remote diagnostic measures may be considered as appropriate (see Section 4.2).

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.

Bleeding
The most common complication encountered during METALYSE therapy is bleeding.

The concomitant use of other active substances affecting coagulation or platelet function (e.g., heparin) may contribute to bleeding (see Section 4.3).

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 insertions, 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, 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 of bleeding with expected benefits under the following conditions:

- Patients receiving oral anticoagulant treatment: The use of METALYSE may be considered when appropriate test(s) show no clinically relevant anticoagulant activity
- Prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage
- Recent intramuscular injection or small recent traumas, such as biopsies, puncture of major vessels
- History of previous stroke or transient ischaemic attack (TIA).

Intracerebral haemorrhages represent the most frequent adverse event. However, this had not led to an increased overall morbidity or mortality.

The risk of intracranial haemorrhage in acute ischaemic stroke patients may be increased with the use of METALYSE.

This applies in particular in the following cases:

- All situations involving a high risk of haemorrhage including those listed in Section 4.3
- Late time-to-treatment onset

- Patients pre-treated with aspirin may have a greater risk of intracerebral haemorrhage and/or mortality, particularly if METALYSE treatment is delayed.
- Compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment and may have an increased risk of intracerebral haemorrhage when thrombolysed. In general, the benefit-risk of thrombolysis in patients of advanced age remains positive. Thrombolysis in AIS patients should be evaluated on an individual benefit-risk basis.

Hypersensitivity

Immune-mediated hypersensitivity reactions associated with the administration of METALYSE can be caused by the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients (see also Section 4.3).

No sustained antibody formation to the tenecteplase molecule has been observed after treatment. However, there is no systematic experience with re-administration of METALYSE.

There is also a risk of hypersensitivity reactions mediated through a non-immunological mechanism.

Angio-oedema represents the most common hypersensitivity reaction reported with METALYSE. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors.

Patients treated with METALYSE should be monitored for angio-oedema during and for up to 24h after administration.

If a severe hypersensitivity reaction (e.g. angio-oedema) occurs, appropriate treatment should be promptly initiated. This may include intubation.

Thrombo-embolism

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

Blood pressure monitoring

To initiate thrombolysis, uncontrolled hypertension or systolic blood pressure (BP) > 185 mmHg or diastolic BP > 110 mmHg should be carefully managed.

BP monitoring during the first 24 hours is necessary. Intravenous antihypertensive therapy is recommended if systolic BP > 180 mmHg or diastolic BP > 105 mmHg.

Special patient groups at reduced benefit-risk

The benefit/risk ratio of thrombolytic therapy is considered less favourable in patients who have had a prior stroke or in whom uncontrolled diabetes exists, although still positive in these patients.

The benefit/risk ratio of METALYSE administration should be thoroughly considered in AIS patients with the following conditions:

- rapidly improving symptoms
- extensive infarctions (e.g. NIHSS > 25)
- seizure at the onset of stroke
- recent history of serious head or spinal trauma or major surgery (such as cardiac, thoracic, abdominal, or orthopaedic)
- elevated activated partial thromboplastin time (aPTT) at presentation
- platelet count of less than 100,000/mm^3
- blood glucose < 50 mg/dL or > 400 mg/dL (< 2.8 mmol/L or > 22.2 mmol/L), which must be corrected before treatment initiation.

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Cerebral oedema
Reperfusion of the ischaemic area may induce cerebral oedema in the infarcted zone.

Paediatric population
Safety and efficacy data in children below 18 years of age are not available for METALYSE. Therefore, METALYSE is not recommended for use in children below 18 years of age.

Excipients

METALYSE contains polysorbate 20.

METALYSE 25 mg contains 2.0 mg of polysorbate 20 in each 25 mg vial. Polysorbates may cause allergic reactions.

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 acute ischaemic stroke have been performed.

Drugs affecting coagulation/platelet function
Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding, and should therefore be avoided in the first 24 hours after METALYSE treatment for acute ischaemic stroke (see Section 4.3).

ACE Inhibitors
Concomitant treatment with ACE inhibitors may enhance the risk of experiencing a hypersensitivity reaction (see Section 4.4).

Other medicinal products
Published academic randomised trials involving more than 2,000 patients treated with tenecteplase did not show any clinically relevant interactions with other medicinal products commonly used in patients with AIS.

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 fetus 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 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:

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

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

b. Tabulated list of adverse reactions

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: Adverse reactions classified according to frequency and system organ class

System Organ Class	Adverse Reaction	Frequency
Immune system disorders	anaphylactoid reactions 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	Very common
Eye disorders	eye haemorrhage	Uncommon
Cardiac disorders	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
	retroperitoneal haemorrhage such as - retroperitoneal haematoma	Uncommon
	nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	ecchymosis	Common

System Organ Class	Adverse Reaction	Frequency
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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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

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

Therapy
In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets).

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 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 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

AcT study
The Alteplase Compared to Tenecteplase (AcT) trial, was designed as a pragmatic, registry based, prospective, randomised, open label, controlled trial of intravenous tenecteplase vs. intravenous alteplase to provide evidence that tenecteplase is non-inferior to alteplase in patients with acute ischemic stroke within 4.5 h from last known well otherwise eligible for intravenous thrombolysis as per current guidelines. The trial achieved its primary outcome demonstrating a clinically relevant non inferiority with tenecteplase 0.25 mg/kg (max. 25 mg) vs alteplase 0.9 mg/kg (max. 90 mg): 296 (36.9%) of 802 patients in the tenecteplase group and 266 (34.8%) of 765 in the alteplase group had a modified Rankin Scale (mRS) score of 0-1 at 90-120 days (unadjusted risk difference 2.1% [95% confidence interval (CI) – 2.6 to 6.9], meeting the prespecified non-inferiority threshold of -5%).

Key safety outcomes were symptomatic intracerebral haemorrhage, orolingual angio-oedema, and extracranial bleeding requiring blood transfusion, all occurring within 24 h of thrombolytic administration, and 90-day all-cause mortality.

There were no meaningful differences in the rate of 24 h symptomatic intracerebral haemorrhage. Rates of imaging-defined intracranial haemorrhage (assessed blinded to symptom status and treatment allocation) showed no differences between the two groups, and the imaging-defined rates of type 2 parenchymal haematoma (i.e., haematoma occupying ≥30% of infarct with obvious mass effect) were similar to the observed rates of symptomatic intracerebral haemorrhage in the trial. There were no meaningful differences in the rate of 90-day mortality 90 days from treatment. Orolingual angio-oedema and peripheral bleeding requiring blood transfusion were rare and similar in both groups (see Table 3).

Table 3. Incidence of key safety outcomes in tenecteplase and alteplase group

	Tenecteplase group	Alteplase group	Risk difference (95% CI)
24 h symptomatic intracerebral haemorrhage	27/800 (3.4%)	24/763 (3.2%)	0.2 (-1.5 to 2.0)
Imaging-identified intracranial haemorrhage	154/800 (19.3%)	157/763 (20.6%)	-1.3 (-5.3 to 2.6)
Extracranial bleeding requiring blood transfusions	6/800 (0.8%)	6/763 (0.8%)	0.0 (-0.9 to 0.8)
Death within 90 days of randomisation (n=1554)	122/796 (15.3%)	117/758 (15.4%)	-0.1 (-3.7 to 3.5)
Orolingual angio-oedema	9/800 (1.1%)	9/763 (1.2%)	-0.1 (-1.1 to 1.0)
Parenchymal haematoma type 2 (haematoma occupying ≥30% of infarct with obvious mass effect)	21/800 (2.6%)	18/763 (2.4%)	0.3 (-1.3 to 1.8)

EXTEND-IA TNK study
EXTEND-IA TNK was designed to assess whether tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram when administered within 4.5 h of ischaemic stroke onset in patients planned to undergo endovascular therapy.

Patients with ischaemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy were randomised to receive tenecteplase 0.25 mg/kg or alteplase 0.9 mg/kg within 4.5 h after symptom onset. There were 101 patients in each treatment group. The primary outcome was reperfusion of greater than 50% of the involved ischaemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Non-inferiority of tenecteplase was tested, followed by superiority.

The primary outcome occurred in 22% of the patients treated with tenecteplase vs 10% of those treated with alteplase (incidence difference, 12%; 95% CI 2 to 21; incidence ratio, 2.2; 95% CI 1.1 to 4.4).

Secondary outcomes included the mRS score at 90 days. In an ordinal analysis of the mRS score at 90 days, patients in the tenecteplase group had a median score of 2 (interquartile range, 0 to 3), compared to a median score of 3 (interquartile range, 1 to 4) among patients in the alteplase group (common odds ratio, 1.7; 95% CI, 1.0 to 2.8). The incidence of recovery to independent function (mRS score of 0 to 2 or no change from baseline function) at day 90 occurred in 65 of 101 patients (64%) in the tenecteplase group and in 52 of 101 (51%) in the alteplase group (adjusted incidence ratio, 1.2; 95% CI, 1.0 to 1.5; adjusted odds ratio, 1.8; 95% CI, 1.0 to 3.4).

The proportion of mRS 0-1 at 90 days was 51% for the tenecteplase group and 43% for the alteplase group.

The symptomatic intracerebral haemorrhage (sICH) occurred in 1% of the patients in each group. There were 10 deaths (10%) in the tenecteplase group and 18 (18%) in the alteplase group, which was not significant in the pre-specified logistic-regression analysis. Most of the deaths were related to progression of major stroke (9 in tenecteplase group and 14 in alteplase group). Tenecteplase 0.25 mg/kg showed a similar safety profile compared to alteplase 0.9 mg/kg.

Real World Evidence
Several non-interventional studies compared tenecteplase (0.25 mg/kg) versus alteplase (0.9 mg/kg) in AIS with or without large vessel occlusion (LVO) within 4.5 hours after symptom onset. These observational studies reported adjusted (or propensity score matched) estimates, included in total >2,900 AIS patients (from studies with over 100 patients treated with tenecteplase), and reported a consistent similar safety and effectiveness profile of tenecteplase in comparison with intravenous alteplase. Endpoints measured included functional outcome (3-month mRS score), all-cause mortality, intracranial haemorrhage and symptomatic intracranial haemorrhage, rates of angioedema, door-to needle time, door-in-door out time, imaging-to-thrombolysis time, thrombolysis-to-puncture time, and onset-to-needle time.

5.2 Pharmacokinetic properties

Absorption and distribution
Tenecteplase is an intravenously administered recombinant protein that activates plasminogen. Following intravenous bolus administration of 30 mg tenecteplase in patients with acute myocardial infarction (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.

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 (± SD) volume of distribution at the steady-state (Vss) ranged from 6.3 ± 2 L to 15 ± 7 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 ± 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 then 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

The excipients are arginine, phosphoric acid and polysorbate 20.

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
Chemical and physical in-use stability has been demonstrated 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. Before use, keep in the outer carton in order to protect from light.

6.5 Nature and contents of container

METALYSE 25 mg: 1 vial containing 25 mg (5,000 U) tenecteplase

6.6 Special precautions for disposal and other handling

Instructions for use and handling, and disposal
METALYSE should be reconstituted by adding 5 mL of sterile water for injections to the vial containing the powder for solution for injection using a needle and a syringe (not provided in the package).

1. Remove the crimp cap from the vial.
2. Fill a syringe with 5 mL of sterile water for injections and penetrate the vial stopper in the middle with the needle.
3. Add all the sterile water for injections into the vial by pushing the syringe plunger down slowly to avoid foaming.
4. Keep the syringe attached to the vial and reconstitute by swirling gently.
5. The reconstituted preparation is a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
6. Directly before the solution is administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
7. Transfer the appropriate volume of reconstituted solution of METALYSE into the syringe, based on the patient's weight (see Table 1).

8. 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 vial nor the same venous line (not even with heparin).
9. METALYSE should be administered as a single dose to the patient, intravenously over 5 to 10 seconds. It should not be administered into a line containing dextrose as METALYSE is incompatible with dextrose solution.
10. The line should be flushed after METALYSE injection for proper delivery.
11. Any unused solution should be discarded.

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 76216
Manukau City
Auckland
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Telephone: 0800 802 461

9. DATE OF FIRST APPROVAL

20 February 2025

10. DATE OF REVISION OF THE TEXT

29 January 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Removal of statement regarding patients weighing 50 kg or less Addition of information regarding thrombectomy Editorial changes
4.3	Update to Contraindications Editorial changes
4.4	Update to warnings under the subsections “Bleeding”, “Blood pressure monitoring” and “Special patient groups at reduced benefit-risk” Addition of warning regarding thromboembolism Addition of warning regarding the excipient Polysorbate 20 Editorial changes