SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metalyse 5 000 units (25 mg) powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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.

Excipient(s) with known effect
Each 25 mg vial contains 2.0 mg polysorbate 20 (E 432).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

The powder is white to off-white.

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 Posology and method of administration

Posology

Metalyse must be prescribed by physicians experienced in neurovascular care and the use of thrombolytic treatment, with the facilities to monitor that use.

Treatment with Metalyse must be initiated 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.

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

Metalyse should be administered on the basis of body weight, with a maximum single dose of 5 000 units (25 mg tenecteplase) for the indication acute ischaemic stroke.
Benefit-risk of tenecteplase treatment should be carefully evaluated in patients weighing 50 kg or less due to limited availability of data.

The volume required to administer the correct total dose can be calculated from the following scheme:

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
≥ 90	5 000	25.0	5.0
For details see section 6.6: Special precautions for disposal and other handling			

Elderly (> 80 years)
Metalyse should be administered with caution in the elderly (> 80 years) due to a higher bleeding risk (see information on bleeding in section 4.4).

Paediatric population
The safety and efficacy of Metalyse in children below 18 years of age have not been established. No data are available.

Adjunctive therapy

Drugs affecting coagulation/platelet function
The safety and efficacy of this regimen with concomitant administration of heparin or platelet aggregation inhibitors such as acetylsalicylic acid during the first 24 hours after treatment with Metalyse have not been sufficiently investigated. Therefore, administration of intravenous heparin or platelet aggregation inhibitors such as acetylsalicylic acid 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.

Method of administration

The reconstituted solution should be administered intravenously and is for immediate use. The reconstituted solution is a clear and colourless to slightly yellow solution.

The required dose should be administered as a single intravenous bolus over approximately 5 to 10 seconds.

40 mg and 50 mg vials of tenecteplase are not intended for use in acute ischaemic stroke. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to gentamicin (a trace residue from the manufacturing process).

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

- Significant bleeding disorder either at present or within the past 6 months
- Patients receiving effective anticoagulation (e.g. vitamin K antagonists with INR > 1.7) (see section 4.4, subsection "Bleeding")
- Known history of or suspected intracranial haemorrhage
- Symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal
- Severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques
- Acute ischaemic stroke without disabling neurological deficit, or symptoms rapidly improving before start of injection
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled arterial hypertension (see section 4.4)
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- Recent trauma to the head or cranium
- Bacterial endocarditis, pericarditis
- Acute pancreatitis
- 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
- Administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory
- Patients with any history of prior stroke and concomitant diabetes
- Prior stroke within the last 3 months
- Platelet count of below 100 000/mm3
- Systolic blood pressure > 185 mmHg or diastolic BP > 110 mmHg, or when BP cannot be reduced below these limits by careful management
- Blood glucose < 50 mg/dL (see section 4.4) or > 400 mg/dL (< 2.8 mM or > 22.2 mM)

4.4 Special warnings and precautions for use

Traceability

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

Thrombolytic treatment requires adequate monitoring. Treatment must be performed under the responsibility and follow-up of physicians trained and experienced in neurovascular care and the use of thrombolytic treatments, with the facilities to monitor that use. For the indication verification remote diagnostic measures may be considered as appropriate, see sections 4.1 and 4.2.

Bleeding

The most common complication encountered during tenecteplase therapy is bleeding. The concomitant use of other active substances affecting coagulation or platelet function (e.g. heparin) may contribute to bleeding, see sections 4.2 and 4.3. As fibrin is lysed during tenecteplase therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with tenecteplase.

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

In the following conditions, the risk of tenecteplase therapy may be increased and should be weighed against the anticipated benefits:

- Recent intramuscular injection or small recent traumas, puncture of major vessels
- Patients receiving oral anticoagulants: The use of Metalyse may be considered when appropriate test(s) show no clinically relevant activity on the coagulation system (e.g. INR $\leq$ 1.7 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal), see section 4.3
- Prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage.

Intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke (up to 19 % of patients without any increase of overall morbidity or mortality).
Risk of intracranial haemorrhage in patients with acute ischaemic stroke may be increased with the use of Metalyse.

This applies in particular in the following cases:

- late time to treatment from last known well. Therefore, the administration of Metalyse should not be delayed
- patients pre-treated with acetylsalicylic acid (ASA) 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 individual benefit-risk basis.

<u>Thrombo-embolism</u>

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).

<u>Blood pressure monitoring</u>

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

Special 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 those with known uncontrolled diabetes, but still positive in these patients (see also section 4.3).

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

- Seizure at the onset of stroke. (Thrombolytic therapy in these patients should only be considered when there is no suspicion of a stroke mimic or significant head trauma).
- In patients initially presenting with blood glucose < 50 mg/dL, thrombolysis may be considered after correction to normal blood glucose values, if the diagnosis of AIS persists (see section 4.3).

In stroke patients the likelihood of a favourable outcome decreases with longer time from onset of symptoms to thrombolytic treatment, increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or symptomatic intracranial bleeding increases, independently of treatment.

Cerebral oedema

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

Hypersensitivity/Re-administration

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 sections 4.3 and 6.1.

No sustained antibody formation to the tenecteplase molecule has been observed after treatment. However there is no systematic experience with re-administration of tenecteplase. 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 24 h after administration.

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

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.

Metalyse contains polysorbate 20

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

4.5 Interaction with other medicinal products 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 (when administered prior to, during or after tenecteplase therapy). These products should be avoided in the first 24 hours after Metalyse treatment for acute ischaemic stroke. With regard to pre-treatment with these substances, see sections 4.2, 4.3 and 4.4.

ACE Inhibitors

Concomitant treatment with ACE inhibitors may enhance the risk of experiencing a hypersensitivity reaction, see section 4.4.

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

There is a limited amount of data from the use of Metalyse in pregnant women. Nonclinical data performed with tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the active substance and in a few cases abortion and resorption of the foetus occurred (effects only have been observed with repeated dose administration). Tenecteplase is not considered to be teratogenic (please see section 5.3).

The benefit of treatment must be evaluated against the potential risks during pregnancy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Haemorrhage is the most common undesirable effect associated with the use of tenecteplase. The type of haemorrhage can be superficial at the injection site or internal at any site or body cavity. Death and permanent disability are reported in patients who have experienced bleeding episodes.

Tabulated list of adverse reactions

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

Except for the occurrence of ADR reperfusion arrhythmias in the indication acute myocardial infarction and the frequency of ADR intracranial haemorrhage in the indication acute ischaemic stroke, there is no medical reason to assume that the safety profile of Metalyse in the indication acute ischaemic stroke is different from the profile in the indication acute myocardial infarction.

Table 1 displays the frequency of adverse reactions.

System organ class	Adverse reaction
Immune system disorders	
Rare	Anaphylactoid reaction (including rash, urticaria, bronchospasm, laryngeal oedema)
Nervous system disorders	
Very common	Intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage) including associated symptoms as somnolence, aphasia, hemiparesis, convulsion
Eye disorders	
Uncommon	Eye haemorrhage
Cardiac disorders	
Rare	Pericardial haemorrhage
Vascular disorders	
Very common	Haemorrhage
Rare	Embolism (thrombotic embolisation)
Respiratory, thoracic and mediastinal disorders	
Common	Epistaxis
Rare	Pulmonary haemorrhage
Gastrointestinal disorders	
Common	Gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage)
Uncommon	Retroperitoneal haemorrhage (such as retroperitoneal haematoma)
Not known	Nausea, vomiting

Skin and subcutaneous tissue disorders	
Common	Ecchymosis
Renal and urinary disorders	
Common	Urogenital haemorrhage (such as haematuria, haemorrhage urinary tract)
General disorders and administration site conditions	
Common	Injection site haemorrhage, puncture site haemorrhage
Investigations	
Rare	Blood pressure decreased
Not known	Body temperature increased
Injury, poisoning and procedural complications	
Not known	Fat embolism, which may lead to corresponding consequences in the organs concerned
Surgical and medical procedures	
Not known	Transfusion

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Therapy

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus.

Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects

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

Clinical efficacy and safety

AcT study

The Alteplase Compared to Tenecteplase (AcT) trial, was designed as a pragmatic, registry based, prospective, randomized, controlled, open label trial with blinded endpoint assessment 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 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 an mRS score of 0-1 at 90-120 days (unadjusted risk difference 2.1% [95% CI - 2.6 to 6.9]. Results in the mITT and mPP populations were similar.

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 2).
Table 2. 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 = 1 554)	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, 21; incidence ratio, 2.2; 95% CI 1.1, 4.4).

Secondary outcomes included the mRS score at 90 days. The proportion of mRS 0-1 at 90 days was 51% for the tenecteplase group and 43% for the alteplase group (adjusted incidence ratio 1.2; 95% CI 0.9 to 1.6).

The 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.

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 alteplase.

5.2 Pharmacokinetic properties

Absorption and distribution

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

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

Biotransformation

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

Elimination

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

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

Linearity/Non-Linearity

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

Renal and hepatic impairment

Because elimination of tenecteplase is through the liver, it is not expected that renal dysfunction will affect its the pharmacokinetics. This is also supported by animal data. However, the effect of renal and hepatic dysfunction on pharmacokinetics of

tenecteplase in humans has not been specifically investigated. Accordingly, there is no guidance for the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency.

5.3 Preclinical safety data

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 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 limited to an embryotoxicity study in rabbits, as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

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

Arginine
Concentrated phosphoric acid (E 338)
Polysorbate 20 (E 432)
Trace residue from manufacturing process: Gentamicin

6.2 Incompatibilities

Metalyse is incompatible with glucose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale

3 years

Reconstituted solution

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

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

6.4 Special precautions for storage

Do not store above 30 °C. Keep the container in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL clear glass vial, with a coated (B2-44) grey rubber stopper and a crimp cap filled with powder for solution for injection. Each vial contains 25 mg tenecteplase.

6.6 Special precautions for 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 injection and penetrate the vial stopper in the middle with the needle.
3. Add all the sterile water for injection 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 solution for injection results in 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 Metalyse reconstituted solution into the syringe, based on the patient's weight.

Patients' body weight category (kg)	Volume of reconstituted solution (mL)	Tenecteplase (U)	Tenecteplase (mg)
< 60	3.0	3 000	15.0
≥ 60 to < 70	3.5	3 500	17.5
≥ 70 to < 80	4.0	4 000	20.0
≥ 80 to < 90	4.5	4 500	22.5
≥ 90	5.0	5 000	25.0

8. A pre-existing intravenous line may be used for administration of Metalyse in sodium chloride 9 mg/mL (0.9%) solution only. No other medicinal product should be added to the injection solution.
9. Metalyse is to be administered to the patient, intravenously in about 5 to 10 seconds. It should not be administered in a line containing glucose as Metalyse is incompatible with glucose solution.
10. The line should be flushed after Metalyse injection for a proper delivery.
11. Any unused reconstituted solution should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 14598/0240

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

02/09/2025