SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metalyse 8 000 units (40 mg) powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 8 000 units (40 mg) tenecteplase.
Each pre-filled syringe contains 8 mL solvent.

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 a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.
The solvent is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metalyse is indicated in adults for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Posology

Metalyse should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Metalyse should be initiated as early as possible after onset of symptoms.

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

Metalyse should be administered 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)	Corresponding volume of reconstituted solution (mL)
< 60	6 000	30	6
≥ 60 to < 70	7 000	35	7
≥ 70 to < 80	8 000	40	8
≥ 80 to < 90	9 000	45	9
≥ 90	10 000	50	10
For details see section 6.6: Special precautions for disposal and other handling			

Elderly (≥ 75 years)
Metalyse should be administered with caution in the elderly (≥ 75 years) due to a higher bleeding risk (see information on bleeding in section 4.4 and on the STREAM study in section 5.1).

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

Adjunctive therapy

Antithrombotic adjunctive therapy with platelet inhibitors and anticoagulants should be administered according to the current relevant treatment guidelines for the management of patients with ST-elevation myocardial infarction.
For coronary intervention see section 4.4.

Unfractionated heparin and enoxaparin have been used as antithrombotic adjunctive therapy in clinical studies with Metalyse.

Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued with lifelong treatment unless it is contraindicated.

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 10 seconds.

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). If treatment with Metalyse is nevertheless considered to be necessary, facilities for resuscitation should be immediately available in case of need.

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 oral anticoagulant treatment, e.g. warfarin sodium (INR > 1.3) (see section 4.4, subsection "Bleeding")
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
  (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis
- 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
- Any known history of haemorrhagic stroke or stroke of unknown origin
- Known history of ischaemic stroke or transient ischaemic attack in the preceding 6 months
- Dementia

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.

Coronary intervention

If primary percutaneous coronary intervention (PCI) is scheduled according to the current relevant treatment guidelines, tenecteplase (see section 5.1 ASSENT-4 study) should not be given.

Patients who cannot undergo primary PCI within one hour as recommended by guidelines and receive tenecteplase as primary coronary recanalization treatment should be transferred without delay to a coronary intervention capable facility for angiography and timely adjunctive coronary intervention within 6-24 hours or earlier if medically indicated (see section 5.1 STREAM study).

Bleeding

The most common complication encountered during tenecteplase therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. 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.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

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:

- Systolic blood pressure > 160 mm Hg, see section 4.3
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- 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: The use of Metalyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely and if appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity on the coagulation system (e.g. INR $\leq$ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

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. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) is available when tenecteplase is administered.

GPIIb/IIIa antagonists

Concomitant use of GPIIb/IIIa antagonists increases bleeding risk.

Hypersensitivity/Re-administration

No sustained antibody formation to the tenecteplase molecule has been observed after treatment. However there is no systematic experience with re-administration of tenecteplase. Caution is needed when administering tenecteplase to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients, or to gentamicin (a residue from the manufacturing process). If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, tenecteplase should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

Paediatric population

Metalyse is not recommended for use in children (below 18 years) due to a lack of data on safety and efficacy.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with tenecteplase 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 tenecteplase.

Drugs affecting coagulation/platelet function

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after tenecteplase therapy.

Concomitant use of GPIIb/IIIa antagonists increases bleeding risk.

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 in case of myocardial infarction 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 a very common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious 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).

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	
Uncommon	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	
Uncommon	Reperfusion arrhythmias (such as asystole, accelerated idioventricular arrhythmia, arrhythmia, extrasystoles, atrial fibrillation, atrioventricular first degree to atrioventricular block complete, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with tenecteplase.
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

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

- very common: hypotension, heart rate and rhythm disorders, angina pectoris

- common: recurrent ischaemia, cardiac failure, myocardial infarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon: cardiac arrest, mitral valve incompetence, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare: pulmonary embolism

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

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

Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

ASSENT-2
A large scale mortality trial (ASSENT-2) in approx. 17 000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) 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). 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.

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

ASSENT-4
The ASSENT-4 PCI study was designed to show if in 4 000 patients with large myocardial infarctions pre-treatment with full dose tenecteplase and concomitant single bolus of up to 4 000 IU unfractionated heparin administered prior to primary PCI to be performed within 60 to 180 minutes leads to better outcomes than primary PCI alone. The trial was prematurely terminated with 1 667 randomised patients due to a numerically higher mortality in the facilitated PCI group receiving tenecteplase. The occurrence of the primary endpoint, a composite of death or cardiogenic shock or congestive heart failure within 90 days, was significantly higher in the group receiving the exploratory regimen of tenecteplase followed by routine immediate PCI: 18.6% (151/810) compared to 13.4% (110/819) in the PCI only group, p = 0.0045. This significant difference between the groups for the primary endpoint at 90 days was already present in-hospital and at 30 days.

Numerically all of the components of the clinical composite endpoint were in favour of the PCI only regimen: death: 6.7% vs. 4.9% p = 0.14; cardiogenic shock: 6.3% vs. 4.8% p = 0.19; congestive heart failure: 12.0% vs. 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: re-infarction: 6.1% vs. 3.7% p = 0.0279; repeat target vessel revascularisation: 6.6% vs. 3.4% p = 0.0041.
The following adverse events occurred more frequently with tenecteplase prior to PCI: intracranial haemorrhage: 1% vs. 0% p = 0.0037; stroke: 1.8% vs. 0% p < 0.0001; major bleeds: 5.6% vs. 4.4% p = 0.3118; minor bleeds: 25.3% vs. 19.0% p = 0.0021; blood transfusions: 6.2% vs. 4.2% p = 0.0873; abrupt vessel closure: 1.9% vs. 0.1% p = 0.0001.

STREAM study
The STREAM study was designed to evaluate the efficacy and safety of a pharmaco-invasive strategy versus a strategy of standard primary PCI in patients presenting 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. The pharmaco-invasive strategy consisted of early fibrinolytic treatment with bolus tenecteplase and additional antiplatelet and anticoagulant therapy followed by angiography within 6-24 hours or rescue coronary intervention.

The study population consisted of 1 892 patients 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, re-infarction	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
Re-infarction	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 studies).

** the incidence in the pharmaco-invasive group is as expected for fibrinolysis with tenecteplase (as observed in previous 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 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) versus 10/32 (31.3%) (95% CI: 16.1-50.0), after dose reduction: 25/97 (25.8%) (95% CI: 17.4-35.7) versus 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 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

Powder

Arginine
Concentrated phosphoric acid
Polysorbate 20
Trace residue from manufacturing process: Gentamicin

Solvent

Water for injections

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

20 mL glass vial type I, with a silicone coated grey rubber stopper and a flip-off cap filled with powder for solution for injection. Each vial contains 40 mg tenecteplase.
10 mL plastic pre-filled syringe with 8 mL of solvent.
Sterile vial adapter.

6.6 Special precautions for disposal

Metalyse should be reconstituted by adding the complete volume of solvent from the pre-filled syringe to the vial containing the powder for solution for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (mL)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6 000	30
≥ 60 to < 70	7	7 000	35
≥ 70 to < 80	8	8 000	40
≥ 80 to < 90	9	9 000	45
≥ 90	10	10 000	50

2. Check that the cap of the vial is still intact.
3. Remove the flip-off cap from the vial.
4. Open the top of the vial adapter. Remove the tip-cap from the pre-filled syringe with the solvent. Then immediately screw the pre-filled syringe on the vial adapter tightly and penetrate the vial stopper in the middle with the spike of the vial adapter.
5. Add the solvent 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 solution for injection results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Transfer the appropriate volume of Metalyse reconstituted solution into the syringe, based on the patient's weight.
10. Unscrew the syringe from the vial adapter.
11. 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.
12. Metalyse is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing glucose as Metalyse is incompatible with glucose solution.
13. The line should be flushed after Metalyse injection for a proper delivery.
14. Any unused reconstituted solution should be discarded.

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 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 14598/0197

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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