ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metalyse 8 000 units (40 mg) powder and solvent for solution for injection
Metalyse 10 000 units (50 mg) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metalyse 8 000 units (40 mg) powder and solvent for solution for injection
Each vial contains 8 000 units (40 mg) tenecteplase.
Each pre-filled syringe contains 8 mL solvent.

Metalyse 10 000 units (50 mg) powder and solvent for solution for injection
Each vial contains 10 000 units (50 mg) tenecteplase.
Each pre-filled syringe contains 10 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.

Excipient(s) with known effect
Each 40 mg vial contains 3.2 mg polysorbate 20 (E 432).
Each 50 mg vial contains 4.0 mg polysorbate 20 (E 432).
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. vitamin K antagonists with 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 (see section 4.4)
- 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
- 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
- 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
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- Recent intramuscular injection or small recent traumas, puncture of major vessels
- Advanced age, i.e. patients 75 years or older
- Body weight < 50 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 ≤ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal)
- Prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage

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.

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).

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.

Metalyse contains polysorbate 20

This medicine contains 3.2 mg or 4.0 mg of polysorbate 20 in each 40 mg or 50 mg vial, respectively. Polysorbates may cause allergic reactions.

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 the national reporting system listed in Appendix V.

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 (E 338)
Polysorbate 20 (E 432)
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

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

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.

Metalyse 10 000 units (50 mg) powder and solvent for solution for injection

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 50 mg tenecteplase.
10 mL plastic pre-filled syringe with 10 mL of solvent.

Sterile vial adapter.

6.6 Special precautions for disposal and other handling

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)

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

EU/1/00/169/005

Metalyse 10 000 units (50 mg) powder and solvent for solution for injection

EU/1/00/169/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2001
Date of last renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metalyse 5 000 units (25 mg) powder for solution for injection
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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/mm^3
- 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.

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

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 the national reporting system listed in Appendix V.

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 $\geq$ 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 ratio1.2; 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

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

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 and other handling

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

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2001
Date of last renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach/Riss
Germany

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach/Riss
Germany

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

Powder: Arginine, concentrated phosphoric acid, polysorbate 20
Trace residue from manufacturing process: Gentamicin
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 vial of powder for solution for injection
1 pre-filled syringe of solvent
1 sterile vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution with 8 mL solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Metalyse being administered.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/005

13. BATCH NUMBER

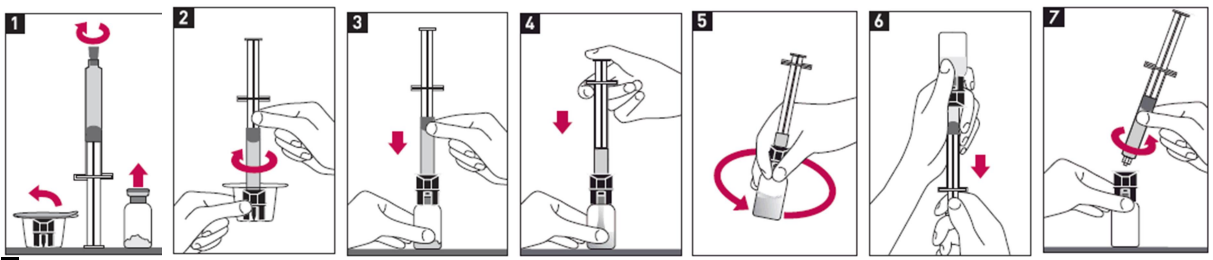
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Particulars to appear on the inner side of the lid of the carton in form of a pictogram

Instructions for use



1 Open the top of the vial-adapter. Remove tip-cap from syringe. Remove the flip-off cap from the vial.
2 Screw prefilled syringe in the vial-adapter tightly.
3 Penetrate the vial stopper in the middle with the spike of the vial-adapter.

4 Add the water for injections by pushing the syringe plunger slowly down to avoid foaming.
5 Keep the syringe attached to the vial and reconstitute by swirling gently.
6 Invert vial/syringe and transfer the appropriate volume of the solution into syringe according to the dosing instructions.
7 Unscrew syringe from the vial-adapter. Now solution is ready for iv. bolus injection.

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Metalyse 8 000 U (40 mg)
powder for solution for injection.
tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 8 000 units (40 mg) tenecteplase.
The reconstituted solution contains 1 000 units (5 mg) tenecteplase per mL.

3. LIST OF EXCIPIENTS

Arginine, concentrated phosphoric acid, polysorbate 20
Trace residue from manufacturing process: Gentamicin

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial of powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV after reconstitution with 8 mL solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Metalyse 8 000 U (40 mg) intravenous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 mL water for injections

6. OTHER

After reconstitution, for patients of body weight (kg):

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Metalyse 10 000 U (50 mg)
powder and solvent for solution for injection
tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 000 units (50 mg) tenecteplase.
Each pre-filled syringe contains 10 mL solvent.
The reconstituted solution contains 1 000 units (5 mg) tenecteplase per mL.

3. LIST OF EXCIPIENTS

Powder: Arginine, concentrated phosphoric acid, polysorbate 20
Trace residue from manufacturing process: Gentamicin
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 vial of powder for solution for injection
1 pre-filled syringe of solvent
1 sterile vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution with 10 mL solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Metalyse being administered.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/006

13. BATCH NUMBER

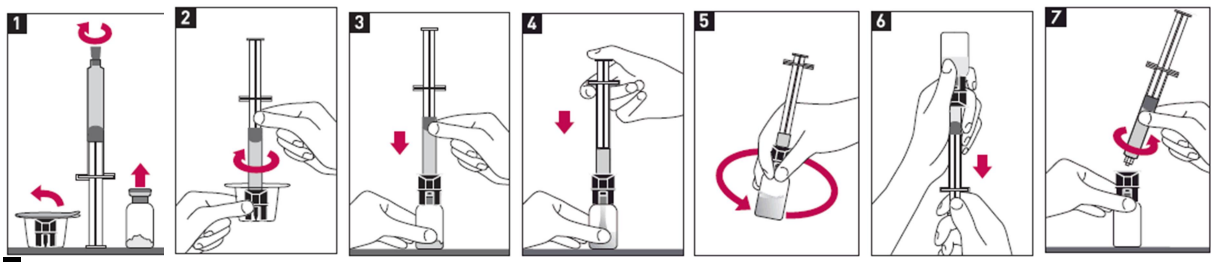
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Particulars to appear on the inner side of the lid of the carton in form of a pictogram

Instructions for use



1 Open the top of the vial-adapter. Remove tip-cap from syringe. Remove the flip-off cap from the vial.
2 Screw prefilled syringe in the vial-adapter tightly.
3 Penetrate the vial stopper in the middle with the spike of the vial-adapter.

4 Add the water for injections by pushing the syringe plunger slowly down to avoid foaming.
5 Keep the syringe attached to the vial and reconstitute by swirling gently.
6 Invert vial/syringe and transfer the appropriate volume of the solution into syringe according to the dosing instructions.
7 Unscrew syringe from the vial-adapter. Now solution is ready for iv. bolus injection.

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Metalyse 10 000 U (50 mg)
powder for solution for injection.
tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 000 units (50 mg) tenecteplase.
The reconstituted solution contains 1 000 units (5 mg) tenecteplase per mL.

3. LIST OF EXCIPIENTS

Arginine, concentrated phosphoric acid, polysorbate 20
Trace residue from manufacturing process: Gentamicin

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial of powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV after reconstitution with 10 mL solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Metalyse 10 000 U (50 mg) intravenous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mL water for injections

6. OTHER

After reconstitution, for patients of body weight (kg):

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Metalyse 5 000 U (25 mg)
powder for solution for injection
tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 000 units (25 mg) tenecteplase and arginine, concentrated phosphoric acid, polysorbate 20.
The reconstituted solution contains 1 000 units (5 mg) tenecteplase per mL.

3. LIST OF EXCIPIENTS

Trace residue from manufacturing process: Gentamicin

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial of powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV after reconstitution with 5 mL sterile water for injection

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Metalyse being administered.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/169/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Metalyse 5 000 U (25 mg)
powder for solution for injection
tenecteplase

2. METHOD OF ADMINISTRATION

IV after reconstitution with 5 mL water for injection

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 vial of powder for solution for injection

6. OTHER

Keep the container in the outer carton in order to protect from light.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Metalyse 8 000 units (40 mg) powder and solvent for solution for injection
Metalyse 10 000 units (50 mg) powder and solvent for solution for injection
tenecteplase

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Metalyse is and what it is used for

Metalyse is a powder and solvent for solution for injection.

Metalyse belongs to a group of medicines called thrombolytic agents. These medicines help to dissolve blood clots. Tenecteplase is a recombinant fibrin-specific plasminogen activator.

Metalyse is used to treat myocardial infarctions (heart attacks) within 6 hours after the onset of symptoms and helps to dissolve the blood clots that have formed in the blood vessels of the heart. This helps to prevent the damage caused by heart attacks and has been shown to save lives.

2. What you need to know before you receive Metalyse

Metalyse will not be prescribed and given by your doctor

– if you have previously had a sudden life-threatening allergic reaction (severe hypersensitivity) to tenecteplase, to any of the other ingredients of this medicine (listed in section 6) or to gentamicin (a trace residue from the manufacturing process). If treatment with Metalyse is nevertheless considered to be necessary, facilities for reanimation should be immediately available in case of need;

– if you have, or have recently had, an illness that increases your risk of bleeding (haemorrhage), including:

- ❖ a bleeding disorder or tendency to bleed (haemorrhage)
- ❖ stroke caused by bleeding in the brain (haemorrhagic stroke) or stroke of unknown cause
- ❖ stroke caused by a blood clot in an artery of the brain (ischaemic stroke) in the preceding 6 months
- ❖ very high, uncontrolled blood pressure
- ❖ a head injury
- ❖ severe liver disease
- ❖ gastric ulcer or ulcers in the gut
- ❖ varicose veins in the gullet (oesophageal varices)

- ❖ abnormality of the blood vessels (e.g. an aneurysm)
- ❖ certain tumours
- ❖ inflammation of the lining around the heart (pericarditis); inflammation or infection of the heart valves (endocarditis)
- ❖ dementia;

– if you are taking tablets/capsules used to ”thin” the blood, such as coumarin derivatives like warfarin (anti-coagulants);
– if you have an inflamed pancreas (pancreatitis);
– if you have recently had major surgery including surgery to your brain or spine.

Warnings and precautions

Your doctor will take special care with Metalyse

– if you have had any allergic reaction other than a sudden life-threatening allergic reaction (severe hypersensitive) to tenecteplase, to any of the other ingredients of this medicine (listed in section 6) or to gentamicin (a trace residue from the manufacturing process);
– if you have high blood pressure;
– if you have had gastrointestinal (gut) or genitourinary bleeding within the last ten days (this may cause blood in stools or urine);
– if you have a heart valve abnormality (e.g. mitral stenosis) with an abnormal heart rhythm (e.g. atrial fibrillation);
– if you have recently had an intramuscular injection;
– if you are aged 75 years or older;
– if you weigh less than 50 kg;
– if you have been given cardiopulmonary resuscitation (chest compressions) for more than 2 minutes duration;
– if you have ever received Metalyse before.

Children and adolescents
The use of Metalyse in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Metalyse
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Metalyse contains polysorbate 20
This medicine contains 3.2 mg or 4.0 mg of polysorbate 20 in each 40 mg or 50 mg vial, respectively. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How is Metalyse administered

The doctor calculates your dose of Metalyse according to your bodyweight, based on the following scheme:

Bodyweight (kg)	less than 60	60 to 70	70 to 80	80 to 90	above 90
Metalyse (U)	6 000	7 000	8 000	9 000	10 000

Your doctor will give you the medicinal product to prevent blood clotting in addition to Metalyse, as soon as possible after your chest pain starts.

Metalyse is given by a single injection into a vein by a doctor who is experienced in the use of this type of medicinal product.

Your doctor will give Metalyse as soon as possible after your chest pain starts as a single dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects described below have been experienced by people given Metalyse:

Very common (may affect more than 1 in 10 people):
- Bleeding

Common (may affect up to 1 in 10 people):
- Bleeding at the injection or puncture site
- Nosebleeds
- Genitourinary bleeding (you may notice blood in your urine)
- Bruising
- Gastro-intestinal bleeding (e.g. bleeding from the stomach or bowel)

Uncommon (may affect up to 1 in 100 people):
- Irregular heart beat (reperfusion arrhythmias), sometimes leading to cardiac arrest. Cardiac (heart) arrest can be life threatening.
- Internal bleeding in the abdomen (retroperitoneal bleeding)
- Bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events
- Bleeding in the eyes (eye haemorrhage)

Rare (may affect up to 1 in 1 000 people):
- Low blood pressure (hypotension)
- Bleeding in the lungs (pulmonary haemorrhage)
- Hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), difficulty breathing (bronchospasm)
- Bleeding into the area surrounding the heart (haemopericardium)
- Blood clot in the lung (pulmonary embolism) and in the vessels of other organ systems (thrombotic embolisation)

Not known (frequency cannot be estimated from the available data):
- Fat embolism (clots consisting of fat)
- Nausea
- Vomiting
- Body temperature increased (fever)
- Blood transfusions as consequence of bleedings

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

Very common (may affect more than 1 in 10 people):
- Low blood pressure (hypotension)
- Irregular heart beat
- Chest pain (angina pectoris)

Common (may affect up to 1 in 10 people):
- Further chest pain/angina (recurrent ischaemia)
- Heart attack
- Heart failure
- Shock due to heart failure
- Inflammation of the lining around the heart
- Fluid in the lungs (pulmonary oedema)

Uncommon (may affect up to 1 in 100 people):
- Heart arrest
- Problem with the heart valve or heart lining (mitral valve incompetence, pericardial effusion)
- Blood clot in the veins (venous thrombosis)
- Fluid between the heart lining and the heart (cardiac tamponade)
- Rupture of the heart muscle (myocardial rupture)

Rare (may affect up to 1 in 1 000 people):
- Blood clot in the lung (pulmonary embolism)

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

In case of bleeding in the brain events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders, palsy of parts of the body (hemiparesis) and fits (convulsions).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Metalyse

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

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

Once Metalyse has been reconstituted it may be stored for 24 hours at 2-8 °C and 8 hours at 30 °C. However, for microbiological reasons your doctor will normally use the reconstituted solution for injection immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Metalyse contains

- The active substance is tenecteplase.
  - Each vial contains 8 000 units (40 mg) of tenecteplase. Each pre-filled syringe contains 8 mL of solvent. When reconstituted with 8 mL solvent each mL contains 1 000 U tenecteplase.

or

– Each vial contains 10 000 units (50 mg) of tenecteplase. Each pre-filled syringe contains 10 mL of solvent. When reconstituted with 10 mL solvent each mL contains 1 000 U tenecteplase.

– The other ingredients are arginine, concentrated phosphoric acid (E 338) and polysorbate 20 (E 432).
– The solvent is water for injections.
– Gentamicin is contained as trace residue from the manufacturing process

What Metalyse looks like and contents of the pack

The carton contains:
– one vial with a lyophilised powder with 40 mg tenecteplase, one ready for use pre-filled syringe with 8 mL solvent and one vial adapter.
or
– one vial with a lyophilised powder with 50 mg tenecteplase, one ready for use pre-filled syringe with 10 mL solvent and one vial adapter.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

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

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach/Riss
Germany

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Package leaflet: Information for the user

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

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Metalyse is and what it is used for

Metalyse is a powder for solution for injection.

Metalyse belongs to a group of medicines called thrombolytic agents. These medicines help to dissolve blood clots. Tenecteplase is a recombinant fibrin-specific plasminogen activator.

Metalyse is used in adults to treat stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke) when it has been less than 4.5 hours since you were last seen without the symptoms of your current stroke.

2. What you need to know before you receive Metalyse

Metalyse will not be prescribed and given by your doctor

– if you have previously had a sudden life-threatening allergic reaction (severe hypersensitivity) to tenecteplase, to any of the other ingredients of this medicine (listed in section 6) or to gentamicin (a trace residue from the manufacturing process). If treatment with Metalyse is nevertheless considered to be necessary, facilities for reanimation should be immediately available in case of need;

– if you have, or have recently had, an illness that increases your risk of bleeding (haemorrhage), including:

- ❖ a bleeding disorder or tendency to bleed (haemorrhage);
- ❖ very high, uncontrolled blood pressure;
- ❖ a head injury;
- ❖ inflammation of the lining around the heart (pericarditis); inflammation or infection of the heart valves (endocarditis);
- ❖ severe liver disease;
- ❖ varicose veins in the gullet (oesophageal varices);
- ❖ gastric ulcer or ulcers in the gut;
- ❖ abnormality of the blood vessels (e.g. an aneurysm);
- ❖ certain tumours;

- ❖ bleeding within the brain or skull;

- if you are taking tablets/capsules used to "thin" the blood (anti-coagulants), unless appropriate test confirmed no clinically relevant activity of such medicine;
- if you have a very severe stroke;
- if your stroke is causing only minor symptoms;
- if the symptoms are rapidly improving before receiving Metalyse;
- if your thromboplastin time (a blood test to see how well your blood clots) is abnormal. This test can be abnormal if you have received heparin (a medicine used to "thin" the blood) within the previous 48 hours;
- if you are diabetic and have ever had a stroke before;
- if you have had a stroke within the last three months;
- if the number of blood platelets (thrombocytes) in your blood is very low;
- if you have a very high blood pressure (above 185/110) which can only be reduced by injection of medicines;
- if the amount of sugar (glucose) in your blood is very low (under 50 mg/dL) or very high (over 400 mg/dL);
- if you have recently had major surgery including surgery to your brain or spine;
- if you have recently had a biopsy (a procedure for obtaining a tissue specimen);
- if you have an inflamed pancreas (pancreatitis).

Warnings and precautions

Your doctor will take special care with Metalyse

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction (severe hypersensitive) to tenecteplase, to any of the other ingredients of this medicine (listed in section 6) or to gentamicin (a trace residue from the manufacturing process);
- if you have or have recently had any other conditions that increase your risk of bleeding, such as:
  - an intramuscular injection
  - a small injury such as a puncture of major vessels
- if you are aged over 80 years, you may have a poorer outcome regardless of treatment with Metalyse.
  However, in general the benefit-risk of Metalyse in patients over 80 years is positive and age alone is not a barrier to treatment with Metalyse;
- if you have been given cardiopulmonary resuscitation (chest compressions) for more than 2 minutes duration;
- if you have ever had a stroke caused by a blood clot in an artery of the brain (ischaemic stroke);
- if you have a heart valve abnormality (e.g. mitral stenosis) with an abnormal heart rhythm (e.g. atrial fibrillation);
- if you have high blood pressure;
- if you had cramps (convulsions) when your stroke started;
- if you are diabetic;
- if the signs of acute ischaemic stroke continues after normalisation of low sugar amount in your blood, your doctor may still consider thrombolytic treatment.
- if you have ever received Metalyse before.

Children and adolescents
The use of Metalyse in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Metalyse
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is particularly important that you tell your doctor if you are taking or have recently taken:
- any medicines which are used to "thin" the blood

- certain medicines used to treat high blood pressure (ACE inhibitors).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Metalyse contains polysorbate 20
This medicine contains 2.0 mg of polysorbate 20 in each 25 mg vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How is Metalyse administered

The doctor calculates your dose of Metalyse according to your bodyweight, based on the following scheme:

Bodyweight (kg)	less than 60	60 to 70	70 to 80	80 to 90	above 90
Metalyse (U)	3 000	3 500	4 000	4 500	5 000

Metalyse is given by a single injection into a vein by a doctor who is experienced in the use of this type of medicinal product.

Your doctor will give Metalyse as soon as possible after your stroke starts as a single dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

<u>The side effects described below have been experienced by people given Metalyse:</u>

Very common (may affect more than 1 in 10 people):
- Bleeding
- Bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events

Common (may affect up to 1 in 10 people):
- Bleeding at the injection or puncture site
- Nosebleeds
- Genitourinary bleeding (you may notice blood in your urine)
- Bruising
- Gastro-intestinal bleeding (e.g. bleeding from the stomach or bowel)

Uncommon (may affect up to 1 in 100 people):
- Internal bleeding in the abdomen (retroperitoneal bleeding)
- Bleeding in the eyes (eye haemorrhage)

Rare (may affect up to 1 in 1 000 people):
- Low blood pressure (hypotension)
- Bleeding in the lungs (pulmonary haemorrhage)
- Hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), difficulty breathing (bronchospasm)
- Bleeding into the area surrounding the heart (haemopericardium)
- Blood clot in the lung (pulmonary embolism) and in the vessels of other organ systems (thrombotic embolisation)

Not known (frequency cannot be estimated from the available data):
- Fat embolism (clots consisting of fat)
- Nausea
- Vomiting
- Body temperature increased (fever)
- Blood transfusions as consequence of bleedings

In case of bleeding in the brain events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders, palsy of parts of the body (hemiparesis) and fits (convulsions).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Metalyse

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

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

Once Metalyse has been reconstituted it may be stored for 24 hours at 2-8 °C and 8 hours at 30 °C. However, for microbiological reasons your doctor will normally use the reconstituted solution for injection immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Metalyse contains

- The active substance is tenecteplase.
  - Each vial contains 5 000 units (25 mg) of tenecteplase. When reconstituted with 5 mL water for injection each mL contains 1 000 U tenecteplase.
- The other ingredients are arginine, concentrated phosphoric acid (E 338) and polysorbate 20 (E 432).
- Gentamicin is contained as trace residue from the manufacturing process

What Metalyse looks like and contents of the pack

The carton contains one vial with a lyophilised powder with 25 mg tenecteplase,

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.