PRODUCT INFORMATION
No. 0245-09
METALYSE®
Powder and solvent for solution for injection

Composition

METALYSE® 10,000 units:
1 vial contains 10,000 units (50 mg) tenecteplase
1 pre-filled syringe contains 10 ml water for injection

The reconstituted solution contains 1,000 units (5 mg) Tenecteplase per ml.

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

Excipients:** L-arginine, phosphoric acid, polysorbate 20
trace residue: gentamicin from manufacturing process

INDICATIONS / USAGE

METALYSE® is indicated for the thrombolytic treatment of Acute Myocardial Infarction (AMI).

Dosage

METALYSE® should be administered as early as possible after symptom onset on the basis of body weight, with a maximum dose of 10,000 units (50 mg Tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme (table 1):

Table 1:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of re-constituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10

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

For coronary intervention please refer to section SPECIAL WARNING AND PRECAUTIONS.

Method of administration

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The reconstituted solution should be administered intravenously and is for immediate use.

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

HANDLING INSTRUCTIONS

METALYSE® should be reconstituted by adding the complete volume of water for injection from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient. (see section DOSAGE AND ADMINISTRATION)

2. Check that the cap of the vial is still intact.

3. Remove the flip-off cap from the vial.

4. Remove the tip-cap from the syringe. Then immediately screw the pre-filled syringe on the vial adapter and penetrate the vial stopper in the middle with the spike of the vial adapter.

5. Add the water for injection into the vial by pushing the syringe plunger down slowly to avoid foaming.

6. Keep the syringe attached to the vial adapter and reconstitute by swirling gently.

7. The reconstituted preparation is a colorless to pale yellow, clear solution. Only clear solution without particles should be used.

8. Directly before the solution is administered, invert the vial with the syringe still attached, so that the syringe is below the vial.

9. Transfer the appropriate volume of reconstituted solution of METALYSE® into the syringe, based on the patient's weight.

10. Unscrew the syringe from the vial adapter.

11. A pre-existing intravenous line, which has been used for administration of 0.9% sodium chloride solution only, may be used for administration of METALYSE®. METALYSE® should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line (not even with heparin).

12. METALYSE® should be administered to the patient, intravenously over 5 to 10 seconds. It should not be administered into a line containing dextrose as METALYSE® is incompatible with dextrose solution.

13. The line should be flushed after METALYSE® injection for proper delivery.

14. Any unused solution should be discarded.

15. Alternatively, the reconstitution can be performed with a needle instead of the included vial adapter.

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Special precautions for in-use storage

Chemical and physical in-use stability

The reconstituted solution has been demonstrated to be stable for 24 hours at 2 – 8° C and for 8 hours at 30° C.

Microbiological in-use stability

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8° C or 8 hours at 30° C.

CONTRAINDICATIONS

METALYSE® is contraindicated in:

- patients with known hypersensitivity to the active substance Tenecteplase, Gentamicin (a trace residue from the manufacturing process) or to any of the excipients
- situations associated with a risk of bleeding such as:
  - significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
  - any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
  - severe uncontrolled arterial hypertension (see section SPECIAL WARNINGS AND PRECAUTIONS)
  - severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
  - active ulcerative gastro-intestinal disease
  - known arterial aneurysm and/or arterial/venous malformation
  - neoplasm with increased bleeding risk
  - bacterial endocarditis, pericarditis
  - acute pancreatitis
  - haemorrhagic stroke or stroke of unknown origin at any time
  - patients receiving effective oral anticoagulant treatment (e.g. vitamin K antagonist with (International Normalized Ratio (INR) > 1.3) (please see section SPECIAL WARNINGS AND PRECAUTIONS, subsection “Bleeding”)
  - major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current acute myocardial infarction), recent trauma to the head or cranium

SPECIAL WARNINGS AND PRECAUTIONS

METALYSE® should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use. This does not preclude the pre-hospital use of METALYSE®. As with other thrombolytics, it is recommended that when METALYSE® is administered standard resuscitation equipment and medication be available in all circumstances.

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Traceability

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

Bleeding

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

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

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

- Patients receiving oral anticoagulants treatment:
  The use of METALYSE® may be considered when appropriate test(s) show no clinically relevant anticoagulant activity.
- Prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage.
- Recent intramuscular injection or small recent traumas, such as biopsies, puncture of major vessels.
- History of previous stroke or transient ischaemic attack (TIA).
- Systolic blood pressure > 160 mm Hg, see also section CONTRAINDICATIONS
- Recent gastro-intestinal or genitourinary bleeding (within the past 10 days)
- Advanced age, i.e. patients 75 years or older
- Body weight < 50 kg

Hypersensitivity

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

Anaphylactoid reactions associated with the administration of METALYSE® are rare and can be caused by hypersensitivity to the active substance Tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. If an anaphylactoid reaction occurs, the injection should be discontinued and appropriate treatment should be initiated.

Thrombo-embolism

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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).

Coronary intervention

Transfer to a coronary intervention capable facility for adjunctive Percutaneous Coronary Intervention (PCI):
Patients receiving METALYSE® as primary coronary recanalization treatment should be transferred without delay to a coronary intervention capable facility for angiography and timely coronary intervention within 6-24 hours or earlier if medically indicated (please refer to section Pharmacological properties).

Primary Percutaneous Coronary Intervention (PCI)
If primary PCI is scheduled according to the current relevant treatment guidelines METALYSE® as administered in the ASSENT-4 PCI study (please see section Pharmacological properties) should not be given.

Arrhythmias
Coronary thrombolysis may result in arrhythmia associated with reperfusion.
Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

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

Excipient(s)

METALYSE® contains polysorbate 20

This medicine contains 4.0 mg of polysorbate 20 in each 50 mg vial. Polysorbates may cause allergic reactions.

USE IN SPECIFIC POPULATION

Pregnancy, Lactation, and Fertility

Pregnancy
There is a limited amount of data from the use of METALYSE® in pregnant women.
Nonclinical studies performed with Tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the drug and in a few cases abortion and resorption of the foetus occurred (effects only have been observed with repeated dose administration). Tenecteplase is not considered to be teratogenic (see Toxicology).
The benefit of treatment must be evaluated against the potential risks in case of myocardial infarction during pregnancy.

Lactation:
It is not known if Tenecteplase is excreted into 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 for the first 24 hours after administration of METALYSE.

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Fertility:
Clinical data as well as nonclinical studies on fertility are not available for Tenecteplase (METALYSE).

INTERACTIONS

No formal interaction studies with METALYSE® and medicinal products commonly administered in patients with acute myocardial infarction (AMI).

Drugs affecting coagulation/platelet function

Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after METALYSE® therapy, see section CONTRAINDICATIONS.

Other medicinal products
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 acute myocardial infarction (AMI) and concomitantly used with METALYSE®.

ADVERSE REACTIONS

As with other thrombolytic agents, haemorrhage is the most common adverse reaction associated with the use of METALYSE. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.
The type of haemorrhage associated with thrombolytic therapy can be divided into two broad categories:

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

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

List of Adverse Reaction

Table 1. Frequency categories:

very common	≥ 1/10
common	≥ 1/100 - < 1/10
uncommon	≥ 1/1,000 - < 1/100
rare	≥ 1/10,000 - < 1/1,000
very rare	< 1/10,000
not known	cannot be estimated from the available data

The above mentioned frequency categories are based on the EU SmPC Guideline (September 2009); therefore, in countries outside the European Union other definitions may be appropriate.

Table 2. Adverse reactions listed in the CCDS and corresponding frequencies according to the EU SmPC guideline

MedDRA	***Tenecteplase adverse reactions using CCDS verbatim term***	***Frequencies according to EU SmPC guideline***

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System Organ Class terminology		
Immune system disorders	anaphylactoid reaction - rash - urticaria - bronchospasm - laryngeal oedema	rare
Nervous system disorders	intracranial haemorrhage - cerebral haemorrhage - cerebral haematoma - haemorrhagic stroke - haemorrhagic transformation stroke - intracranial haematoma - subarachnoid haemorrhage	uncommon
Eye disorders	eye haemorrhage	uncommon
Cardiac disorders	reperfusion arrhythmia such as - asystole - accelerated idioventricular arrhythmia - arrhythmia - extrasystoles - atrial fibrillation - atrioventricular first degree - atrioventricular block complete - bradycardia - tachycardia - ventricular arrhythmia - ventricular fibrillation - ventricular tachycardia occur in close temporal relationship to treatment with METALYSE.	uncommon
	pericardial haemorrhage	rare
	Cardiac arrest	not known
Vascular disorders	haemorrhage	very common
	embolism	rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Common
	pulmonary haemorrhage	Rare
Gastrointestinal disorders	gastrointestinal haemorrhage - gastric haemorrhage - gastric ulcer haemorrhage - rectal haemorrhage - haematemesis - melaena - mouth haemorrhage	common
	nausea	not known
	vomiting	not known
	retroperitoneal haemorrhage - retroperitoneal haematoma	uncommon

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Skin and subcutaneous tissue disorders	ecchymosis	common
Renal and urinary disorders	urogenital haemorrhage such as: - haematuria - haemorrhage urinary tract	common
General disorders and administration site conditions	injection site haemorrhage, puncture site haemorrhage	common
Investigations	blood pressure decreased	rare
	body temperature increased	not known
Injury, poisoning and procedural complications	fat embolism, **which may lead to corresponding consequences in the organs concerned**	not known
Surgical and medical procedures	transfusion	not known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the 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 following contact: Telephone: +62 21 21684084 Or Email: IDsafety@zuelligpharma.com

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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antithrombotic agents
ATC code: B01AD11

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

Pharmacodynamic
After administration of Tenecteplase dose dependent consumption of a2-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,

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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 trials

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

ASSENT 2 study

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) and that the use of Tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% versus 28.9%, p = 0.0003). The reduction of the risk of bleeding is likely to be related to the increased fibrin specificity of Tenecteplase and to its weight adapted regimen.

This translates into a significantly lower need of transfusions (4.3% versus 5.5%,p = 0.0002). Intracranial haemorrhage occurred at a rate of 0.93% versus 0.94% for Tenecteplase and alteplase, respectively. In the 475 patients treated beyond 6 hours numerical differences in favour of Tenecteplase were observed with regard to 30-day mortality (4.3% versus 9.6%), stroke (0.4% versus 3.3%) and ICH (0% versus 1.7%).

ASSENT-4 PCI study

The ASSENT-4 PCI study was designed to show if in 4000 patients with large myocardial infarctions pre-treatment with full dose Tenecteplase and concomitant single bolus of up to 4,000 IU unfractionated heparin administered prior to primary Percutaneous Coronary Intervention (PCI) to be performed within 60 to 180 minutes leads to better outcomes than primary PCI alone. The trial was prematurely terminated with 1667 randomised patients due to a numerically higher mortality in the facilitated PCI group receiving Tenecteplase. The occurrence of the primary endpoint, a composite of death or cardiogenic shock or congestive heart failure within 90 days, was significantly higher in the group receiving the exploratory regimen of Tenecteplase followed by routine immediate PCI: 18.6% (151/810) compared to 13.4% (110/819) in the PCI only group, p = 0.0045. This significant difference between the groups for the primary endpoint at 90 days was already present in-hospital and at 30 days. Numerically, all of the components of the clinical composite endpoint were in favour of the PCI only regimen: death: 6.7% versus 4.9% p = 0.14; cardiogenic shock: 6.3% versus 4.8% p = 0.19; congestive heart failure: 12.0% versus 9.2% p = 0.06 respectively. The secondary endpoints re-infarction and repeat target vessel revascularisation were significantly increased in the group pre-treated with Tenecteplase: reinfarction: 6.1% versus 3.7% p = 0.0279; repeat target vessel revascularisation: 6.6% versus 3.4% p = 0.0041.

The following adverse events occurred more frequently with Tenecteplase prior to PCI: intracranial haemorrhage: 1% versus 0% p = 0.0037; stroke: 1.8% versus 0% p < 0.0001; major bleeds: 5.6% versus 4.4% p = 0.3118; minor bleeds: 25.3% versus 19.0% p = 0.0021; blood transfusions: 6.2% versus 4.2% p = 0.0873; abrupt vessel closure: 1.9% versus 0.1% p = 0.0001.

STREAM study

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

The study population consisted of patients with ST elevation acute myocardial infarction within 3

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hours of onset of symptoms not able to undergo primary PCI within one hour of first medical contact. A sample size of approximately 1000 patients per treatment group was planned for this exploratory study. After 382 patients had been enrolled (19.5 % of the planned study population), the dose of the Tenecteplase bolus was reduced by half for the patients ≥ 75 years because of a higher incidence of intracranial haemorrhage (ICH) in this sub-group.

1892 patients were randomised by means of an interactive voice response system. The primary endpoint, a composite of death or cardiogenic shock or congestive heart failure or re-infarction within 30 days was observed in 12.4% (116/939) of the pharmaco-invasive arm versus 14.3% (135/943) in the primary PCI arm (relative risk 0.86 (0.68-1.09)).

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

	Pharmaco-invasive (n=944)	**Primary PCI (n=948)**	**P**
Composite death, shock, congestive heart failure, reinfarction	116/939 (12.4%)	135/943 (14.3%)	0.21
All-cause mortality	43/939 (4.6%)	42/946 (4.4%)	0.88
Cardiogenic shock	41/939 (4.4%)	56/944 (5.9%)	0.13
Congestive heart failure	57/939 (6.1%)	72/943 (7.6%)	0.18
Reinfarction	23/938 (2.5%)	21/944 (2.2%)	0.74
Cardiac mortality	31/939 (3.3%)	32/946 (3.4%)	0.92

The observed incidence of major and of minor non-ICH bleeds were similar in both groups:

	Pharmaco-invasive (n=944)	Primary PCI (n=948)	P
Major non-ICH bleed	61/939 (6.5%)	45/944 (4.8%)	0.11
Minor non-ICH bleed	205/939 (21.8%)	191/944 (20.2%)	0.40

Incidence of total strokes and intracranial haemorrhage

	Pharmaco-invasive (n=944)	**Primary PCI (n=948)**	**P**
Total stroke (all types)	15/939 (1.6%)	5/946 (0.5%)	0.03*
Intracranial haemorrhage	9/939 (0.96%)	2/946 (0.21%)	0.04**
Intracranial haemorrhage after protocol amendment to half dose in patients ≥ 75 years :	4/747 (0.5%)	2/758 (0.3%)	0.45

* the incidences in both groups are those expected in STEMI patients treated by fibrinolytics or primary PCI (as observed in previous clinical studies).
** the incidence in the pharmaco-invasive group is as expected for fibrinolysis with Metalyse (as observed in previous clinical studies).

None of the differences between groups displayed in the above tables reached the threshold of statistical significance except for the incidence of total strokes and ICH, however the incidences in the pharmaco-invasive group were as observed in previous clinical studies.
After the dose reduction of Tenecteplase by half in patients ≥ 75 years there was no further intracranial hemorrhage (0 of 97 patients) (95% CI: 0.0- 3.7) versus 8.1% (3 of 37 patients) (95% CI: 1.7- 21.9) prior

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to the dose reduction. The bounds of the confidence interval of the observed incidences prior and after dose reduction are overlapping.
In patients ≥ 75 years the observed incidence of the primary efficacy composite end point for the pharmaco-invasive strategy and primary PCI were as follows: before dose reduction 11/37 (29.7%) (95% CI: 15.9- 47.0) vs. 10/32 (31.3%) (95% CI: 16.1-50.0), after dose reduction: 25/97 (25.8%) (95% CI: 17.4-35.7) vs. 25/88 (24.8%) (95% CI: 19.3-39.0). In both groups the bounds of the confidence interval of the observed incidences prior and post dose reduction are overlapping.

PHARMACOKINETICS

Absorption and distribution
Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Following i.v. bolus administration of 30 mg Tenecteplase in patients with acute myocardial infarction, the initially estimated Tenecteplase plasma concentration was 6.45 ± 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.

Metabolism
Tenecteplase is cleared from the circulation by binding to specific receptors in the liver followed by catabolism to small peptide. 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.

Special populations
Renal and hepatic impairment
Because elimination of Tenecteplase is through the liver, it is not expected that renal dysfunction will affect the pharmacokinetics of METALYSE®. This is also supported by animal data. However, the effect of renal and hepatic dysfunction on pharmacokinetics of Tenecteplase in humans has not been specifically investigated.

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TOXICOLOGY

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

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

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

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

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

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Availability

Vial with 50 mg powder for solution for injection + pre-filled syringe with 10 ml water for injections

Reg. No. DKI2452504744A1

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Store bellow 30° C.
Store in a safe place out of the reach of children!

Only on doctor's prescriptions.
Harus dengan resep dokter.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.KG
Ingelheim am Rhein, Germany

Imported by:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Version: 09-1225

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Informasi Produk untuk Pasien
METALYSE® 10 000 Unit (50 mg) serbuk untuk larutan untuk injeksi
Tenecteplase

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisikan informasi penting untuk Anda.
- Simpanlah leaflet ini. Suatu saat Anda mungkin perlu membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Bila Anda mengalami efek samping obat, bicarakan kepada dokter atau apoteker Anda, termasuk efek samping obat yang tidak terdaftar dalam leaflet ini. Lihat bagian 4.

Apa saja yang terdapat dalam leaflet ini

1. Apakah METALYSE® dan digunakan untuk apa
2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan METALYSE®
3. Bagaimana cara menggunakan METALYSE®
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan METALYSE®
6. Isi paket dan informasi lainnya

1. Apakah itu METALYSE® dan digunakan untuk apa

Metalyse berupa serbuk dan pelarut untuk larutan injeksi.

Metalyse termasuk dalam kelompok obat yang disebut agen trombolitik. Obat-obatan ini membantu memecahkan bekuan darah. Tenecteplase adalah aktivator plasminogen spesifik fibrin rekombinan.

Metalyse digunakan untuk pengobatan trombolitik infark miokard akut (IMA)

2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan METALYSE®

Metalyse tidak akan diresepkan dan diberikan oleh dokter Anda

- jika Anda sebelumnya pernah mengalami reaksi alergi mendadak yang mengancam jiwa (hipersensitif berat) terhadap tenecteplase, terhadap salah satu bahan lain dalam obat ini (tercantum dalam bagian 6) atau terhadap gentamicin (residu dari proses pembuatan). Jika pengobatan dengan Metalyse tetap dianggap perlu, fasilitas untuk reanimasi harus segera tersedia jika diperlukan;

- jika Anda menderita, atau baru saja menderita penyakit yang meningkatkan risiko pendarahan (*haemorrhage*), termasuk:

  - kelainan pendarahan atau kecenderungan untuk berdarah (*hemorrhage*)
  - stroke (*cerebrovascular event*)
  - tekanan darah sangat tinggi dan tidak terkontrol
  - cedera kepala
  - penyakit hati yang parah
  - tukak lambung (*peptic ulcer*)
  - varises di kerongkongan (*oesophageal varices*)
  - kelainan pembuluh darah (*e.g. an aneurysm*)
  - tumor tertentu
  - radang pada lapisan di sekitar jantung (*pericarditis*); radang atau infeksi pada katup jantung (*endocarditis*)
  - demensia

- Jika Anda mengonsumsi tablet/kapsul yang digunakan untuk "mengencerkan" darah, seperti turunan kumarin seperti warfarin (antikoagulan);
- Jika Anda mengalami radang pankreas (pankreatitis);

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- Jika Anda baru saja menjalani operasi besar termasuk operasi otak atau tulang belakang;
- Jika Anda telah menjalani resusitasi jantung paru (kompresi dada) selama lebih dari 2 menit, dalam dua minggu terakhir.

Peringatan dan Perhatian

Dokter Anda akan melakukan perawatan khusus dengan Metalyse

- jika Anda pernah mengalami reaksi alergi selain reaksi alergi mendadak yang mengancam jiwa (hipersensitif berat) terhadap tenecteplase, terhadap bahan lain dari obat ini (tercantum dalam bagian 6) atau terhadap gentamisin (residu jejak dari proses pembuatan);
- jika Anda memiliki tekanan darah tinggi;
- jika Anda memiliki masalah dengan sirkulasi darah di otak (*cerebrovascular disease*);
- jika Anda pernah mengalami pendarahan gastrointestinal (*gut*) atau genitourinari dalam sepuluh hari terakhir (ini dapat menyebabkan darah dalam tinja atau urin);
- jika Anda memiliki kelainan katup jantung (misalnya stenosis mitral) dengan irama jantung yang tidak normal (misalnya fibrilasi atrium);
- jika Anda telah menerima suntikan intramuskular ;
- jika Anda berusia di atas 75 tahun;
- jika berat badan Anda kurang dari 50 kg
- jika Anda pernah menerima Metalyse sebelumnya.
- Resusitasi jantung paru atau pijat jantung yang berkepanjangan (> 2 menit).
- Penggunaan Metalyse meningkatkan risiko kejadian penyumbatan aliran darah akibat gumpalan.
- Perawatan khusus diperlukan jika anda menerima tindakan yang disebut Percutaneous Coronary Intervention (PCI)

Obat-obatan Lainnya dan Metalyse
Beri tahu dokter atau apoteker Anda jika Anda sedang mengonsumsi obat lain, baru saja mengonsumsi obat lain, atau mungkin mengonsumsi obat lain.
Penggunaan bersama obat jenis Glyco-ProteinIIb/IIIa antagonists dapat meningkatkan perdarahan.

Kehamilan dan Menyusui
Kehamilan
Jika Anda sedang hamil atau menyusui, merasa mungkin sedang hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter Anda sebelum Anda diberi obat ini.
Pengalaman penggunaan METALYSE pada ibu hamil masih sangat terbatas.
Pada penelitian hewan, obat tenecteplase dapat menyebabkan perdarahan pada induk hewan sampai menyebabkan kematian, dan pada beberapa kasus terjadi keguguran atau janin tidak berkembang. Efek-efek ini muncul karena cara kerja obat, terutama bila diberikan berulang kali.
Namun, tenecteplase tidak terbukti menyebabkan cacat bawaan pada janin.

Jika serangan jantung terjadi pada masa kehamilan, dokter akan mempertimbangkan manfaat pengobatan dibandingkan kemungkinan risikonya.

Menyusui
Belum diketahui apakah tenecteplase keluar melalui ASI.
Karena itu, perlu kehati-hatian jika METALYSE diberikan kepada ibu menyusui. Dokter dapat menyarankan untuk menghentikan menyusui selama 24 jam pertama setelah pemberian obat.

Kesuburan
Belum ada data dari penelitian pada manusia maupun hewan mengenai pengaruh tenecteplase terhadap kesuburan.

Overdosis
Jika obat diberikan terlalu banyak, risiko perdarahan akan meningkat.

Penanganan
Jika terjadi perdarahan hebat dan berkepanjangan, dokter dapat memberikan terapi pengganti (misalnya pemberian produk darah atau obat tertentu) sesuai kebutuhan.

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3. Bagaimana cara menggunakan METALYSE®

Dokter menghitung dosis Metalyse sesuai dengan berat badan Anda, berdasarkan skema berikut:

Berat Badan (kg)	Kurang dari 60	60 to 70	70 to 80	80 to 90	Di atas 90
Metalyse (U)	6 000	7 000	8 000	9 000	10 000

Dokter Anda akan memberikan Anda produk obat untuk mencegah pembekuan darah bersamaan dengan Metalyse, sesegera mungkin setelah nyeri dada Anda mulai.

Metalyse diberikan melalui suntikan tunggal ke dalam pembuluh darah oleh dokter yang berpengalaman dalam penggunaan jenis produk obat ini.

Dokter Anda akan memberikan Metalyse sesegera mungkin setelah nyeri dada Anda mulai sebagai dosis tunggal.

4. Kemungkinan efek samping

Seperti semua obat, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang dijelaskan di bawah ini telah dialami oleh orang yang diberi Metalyse:

Sangat Umum (dapat mempengaruhi lebih dari 1 dari 10 orang):
- Pendarahan

Umum (dapat memengaruhi hingga 1 dari 10 orang):
- Pendarahan di tempat suntikan atau tusukan
- Mimisan
- Pendarahan saluran kemih (Anda mungkin melihat darah dalam urin)
- Memar
- Pendarahan gastrointestinal (misalnya pendarahan dari lambung atau usus)

Tidak umum (dapat memengaruhi hingga 1 dari 100 orang):
- Detak jantung tidak teratur (aritmia reperfusi), terkadang menyebabkan serangan jantung. Serangan jantung dapat mengancam jiwa.
- Pendarahan internal di perut (perdarahan retroperitoneal)
- Pendarahan di otak (perdarahan otak). Kematian atau cacat permanen dapat terjadi setelah pendarahan di otak atau kejadian pendarahan serius lainnya
- Pendarahan di mata (perdarahan mata)

Jarang (dapat memengaruhi hingga 1 dari 1.000 orang):
- Tekanan darah rendah (hipotensi)
- Pendarahan di paru-paru (perdarahan paru)
- Hipersensitivitas (reaksi anafilaktoid) misalnya ruam, gatal-gatal (urtikaria), kesulitan bernapas (bronkospasme)
- Pendarahan di area sekitar jantung (hemoperikardium)
- Gumpalan darah di paru-paru (emboli paru) dan di pembuluh sistem organ lainnya (embolisasi trombotik)

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
- Emboli lemak (gumpalan yang terdiri dari lemak)
- Mual
- Muntah
- Suhu tubuh meningkat (demam)
- Transfusi darah akibat pendarahan

Kejadian kardiovaskular dapat mengancam jiwa dan dapat berujung pada kematian.
Jika terjadi pendarahan otak, kejadian yang berhubungan dengan sistem saraf terjadi, misalnya mengantuk (somnolen), gangguan bicara, kelumpuhan beberapa bagian tubuh (hemiparesis), dan kejang (konvulsi).

Pelaporan efek samping

Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau kondisi

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tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut: Telepon: +62 21 21684084 atau Email IDsafety@zuelligpharma.com

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan METALYSE®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada label dan karton setelah EXP.

Jangan simpan di atas suhu 30 °C.
Simpan produk di dalam karton kemasan untuk melindungi dari cahaya.

Setelah Metalyse dilarutkan, obat dapat disimpan selama 24 jam pada suhu 2-8 °C dan 8 jam pada suhu 30 °C.
Namun, untuk alasan mikrobiologis, dokter Anda biasanya akan segera menggunakan larutan injeksi yang telah dilarutkan.

Jangan membuang obat- obatan apapun melalui air limbah atau limbah rumah tangga.
Tanyakan kepada apoteker Anda cara membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apa saja Isi Metalyse
Zat aktif yang terkandung dalam produk adalah tenecteplase.

Setiap vial berisi 10.000 unit (50 mg) tenecteplase. Setiap jarum suntik yang telah diisi sebelumnya berisi 10 mL pelarut.
Bila dilarutkan dengan 10 mL pelarut, setiap mL berisi 1.000 U tenecteplase.
Bahan tambahan lainnya adalah arginin, asam fosfat pekat dan polisorbat 20. Pelarut yang digunakan adalah air untuk injeksi. Adapun Gentamisin yang terkandung sebagai residu dari proses pembuatan. Polysorbate dapat menyebabkan reaksi alergi.

Seperti apa bentuk METALYSE® Dan isi kemasannya

Dalam satu dus karton berisi:
satu vial berisi serbuk kering dengan tenecteplase 50 mg, dalam satu pre-filled syringe siap pakai dengan pelarut 10 mL dan satu adaptor vial.

Reg.No. DKI2452504744A1

Diproduksi oleh:
Boehringer Ingelheim Pharma GmbH & Co.KG
Ingelheim am Rhein, Germany

Diimpor oleh:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Version: 09-1225

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