PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Metalyse® 8000 U & 10 000 U

Boehringer Ingelheim

Metalyse® solvent

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METALYSE 8 000 U

1 Vial contains 8 000 units (40 mg) tenecteplase.
1 Pre-filled syringe (METALYSE solvent) contains 8 mL of water for injection.

METALYSE 10 000 U

1 Vial contains 10 000 units (50 mg) tenecteplase.
1 Pre-filled syringe (METALYSE solvent) contains 10 mL of 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.

Sugar free.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

METALYSE powder: Clear glass vial with grey rubber stopper containing a white to pale yellow cake of powder.
METALYSE Solvent: Clear, colourless liquid in 10 mL transparent plastic syringe with grey stopper.
Reconstitution results in a colourless to slightly yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METALYSE is indicated for the thrombolytic treatment of acute phase of myocardial infarction (AMI).

4.2 Posology and method of administration

Posology

Treatment should be initiated as early as possible after symptom onset. Insufficient data exist to recommend use of METALYSE beyond 6 - 9 hours after the onset of AMI. There is no information on administration later than 9 hours after MI.

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 table:

Patient's body weight category (kg)	Corresponding volume of re-constituted 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

Method of administration

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

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

Adjunct 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 4.4.

4.3 Contraindications

- Patients with known hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients
- Previous treatment with Tenecteplase
- Subjects > 80 years of age or < 18 years of age
- Pregnancy and lactation (see section 4.6, subsection "lactation")
- Thrombolytic therapy is associated with a risk of bleeding, therefore, METALYSE is contraindicated in the following situations:
    - Hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis. METALYSE is metabolised by the liver and no studies in patients with impaired liver function are available at present
    - Manifest or recent severe or dangerous bleeding disorder either at present or within the last 6 months
    - Patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (international normalised ratio (INR) > 1,3) (see section 4.4, subsection "Bleeding")
    - Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
    - Haemorrhagic stroke or stroke of unknown origin at any time

- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months
- Known haemorrhagic diathesis
- Severe uncontrolled arterial hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes) in the last 2 weeks
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Parturition within the previous 3 days
- Cardiogenic shock
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis.

4.4 Special warnings and precautions for use

The decision to treat a patient with acute myocardial infarction with METALYSE should only be made by a doctor experienced in the use of thrombolytic treatment. This does not preclude the pre-hospital use of METALYSE. When METALYSE is administered standard resuscitation equipment and medication must be available in all circumstances.

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

Bleeding can occur. The most frequent adverse events associated with the use of METALYSE are haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding. Intracranial haemorrhage (ICH) has been observed.

The concomitant use of unfractionated heparin anticoagulation may contribute to bleeding. 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:

- Systolic blood pressure > 160 mmHg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus e.g. mitral stenosis with atrial fibrillation
- Haemostatic defects including those secondary to severe hepatic disease
- Any known recent intramuscular injection (in the last 2 days)
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg
- Patients receiving oral anticoagulant treatment: The use of METALYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.

Re-administration
See section 4.3.

Hypersensitivity
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.

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.

Primary Percutaneous Coronary Intervention (PCI):
If primary PCI is scheduled according to the current relevant treatment guidelines, METALYSE should not be given.

Dysrhythmias
Coronary thrombolysis may result in dysrhythmia associated with reperfusion. Reperfusion dysrhythmias may lead to cardiac arrest, can be life-threatening and may require the use of conventional antidysrhythmic therapies.

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

Cardiac Events
Patients with AMI can, independent of the treatment given, experience disease-related events such as cardiogenic shock, pulmonary oedema, heart failure, cardiac arrest, recurrent ischaemia, reinfarction, myocardial rupture, pericarditis, pericardial effusion, cardiac tamponade, mitral regurgitation, venous thrombosis and electromechanic dissociation.

4.5 Interaction with other medicines and other forms of interaction
METALYSE is incompatible with dextrose solution.
No formal interaction studies with METALYSE 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 METALYSE.

Medicines 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 4.3.

4.6 Fertility, pregnancy and lactation
Pregnancy
There is a limited amount of data from the use of METALYSE in pregnant women (see section 4.3).
Nonclinical studies performed with tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the medicine 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.

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.

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 safety profile

Haemorrhage is the most common undesirable effect 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 bleeding at any site or body cavity.

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

Tabulated summary of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class.

Frequency classes: 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).

System organ class	*Adverse reaction*	*Frequency*
Immune system disorders	Anaphylactoid reaction (including rash, urticaria, bronchospasm, laryngeal oedema)	Rare
Nervous system disorders	Intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage) including associated symptoms as somnolence, aphasia, hemiparesis, convulsion	Uncommon
Eye disorders	Eye haemorrhage	Uncommon
Cardiac disorders	Reperfusion dysrrhythmias (such as asystole, accelerated idioventricular dysrrhythmia, dysrrhythmia, extrasystoles, atrial fibrillation, atrioventricular first degree to atrioventricular block complete, bradycardia, tachycardia, ventricular dysrrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with METALYSE .	Uncommon
	Pericardial haemorrhage	Rare
Vascular disorders	Haemorrhage	Very common

	Embolism	Rare
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common
	Pulmonary haemorrhage	Rare
Gastrointestinal disorders	Gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage)	Common
	Retroperitoneal haemorrhage (such as retroperitoneal haematoma)	Uncommon
	Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Ecchymosis	Common
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

Description of selected adverse reactions

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications https://www.sahpra.org.za.

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 (plasma, platelets) may be considered. (Please refer to section 4.4.)
Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CATEGORY AND CLASS: A 31 Enzymatic preparations

Mechanism of action

Tenecteplase is a recombinant fibrin-specific plasminogen activator. The molecule differs from native tissue-type plasminogen activator (t-PA) by modifications at three sites of the protein structure, thus increasing its fibrin specificity and resistance to inactivation by its endogenous inhibitor. 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.

Pharmacodynamic effects

After administration of tenecteplase dose dependent consumption of α_2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. 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). No clinically relevant antibody formation was detected at 30 days. Although antibodies to tenecteplase were observed 7 to 14 days after therapy, the presence of antibodies after 30 days was less than 1 %.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from the circulation by binding to specific receptors in the liver followed by catabolism to small peptides.

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.

As the kidneys do not appear to be involved in the elimination of tenecteplase, renal dysfunction is not expected to affect the pharmacokinetics. The effect of hepatic dysfunction on the pharmacokinetics of tenecteplase in humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

L-arginine
Phosphoric acid
Polysorbate 20
Trace residue: gentamicin from the manufacturing process.

Solvent

Water for injection

6.2 Incompatabilities

METALYSE is incompatible with dextrose solution.

6.3 Shelf life

Unopened vials

36 months

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.

6.4 Special precautions for storage

Both the vials and the solvent should be stored at or below 30 °C.
Keep the 20 mL glass vial containing METALYSE powder (cake) in the outer carton, as the powder must be protected from light.
Keep out of reach of children.

6.5 Nature and contents of container

Each pack contains: a 20 mL glass vial containing a lyophilised powder cake for preparation of a solution for injection. The powder contains either 8 000 U or 10 000 U of tenecteplase. The vial is fitted with a grey rubber stopper and a flip-off vial cap.

A 10 mL polypropylene syringe with a grey rubber stopper and Luer tip cover, which is pre-filled with water for injection (METALYSE SOLVENT) for reconstitution and a plastic syringe plunger is also included in the pack. The syringe provided with

METALYSE 8 000 U contains 8 mL of solvent and the syringe provided with METALYSE 10 000 U contains 10 mL of solvent.
A vial adapter is also included.

6.6 Special precautions for disposal and other handling

METALYSE should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe of METALYSE solvent 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 (as per the table in section 4.2).
2. Check that the cap of the vial is still intact.
3. Remove the flip-off cap from the vial and open the box of the vial adapter.
4. Remove the tip-cap from the syringe (METALYSE solvent). Then immediately screw the pre-filled syringe (METALYSE solvent) on the vial adapter and penetrate the vial stopper in the middle with the spike of the vial adapter.
5. Add the METALYSE solvent to 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 colourless to slightly yellow, clear solution. Only clear solution without particles should be used.
8. Just before administration, 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. This volume is based on the patient's weight (please refer to the table under sections 4.2).
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 the administration of METALYSE. METALYSE should not be mixed with other medicines, neither in the same infusion-vial nor the same venous line (not even with heparin).
12. METALYSE is to 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.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa

8. REGISTRATION NUMBERS

METALYSE 8 000 U: 34/31/0409
METALYSE 10 000 U: 34/31/0410
METALYSE solvent: 34/32.4/0411

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 04 October 2001.
Date of revision of the text: 30 October 2024

BOTSWANA REG. NO.		
METALYSE 8 000 U/vial	BOT 0600876	S2
METALYSE 10 000 U/vial	BOT 0600877	S2
METALYSE SOLVENT	BOT 0600878	S2

NAMIBIA REG. NO.		
METALYSE 8 000 U/vial	04/31/1377	NS2
METALYSE 10 000 U/vial	04/31/1378	NS2
METALYSE SOLVENT	04/31/1379	NS1

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