APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

Metalyse® 8000 U & 10 000 U

Boehringer Ingelheim

Powder for solution for injection

Metalyse® solvent

Solution for injection

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.
Inactive ingredients: L-arginine, phosphoric acid, polysorbate 20.
Trace residue: gentamicin from manufacturing process.

CATEGORY AND CLASS:

A 31 Enzymatic preparations

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 %.

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.

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

Treatment should be initiated as soon 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.

CONTRAINDICATIONS:
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 WARNINGS AND SPECIAL PRECAUTIONS, 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
- Pregnancy and lactation
- Parturition within the previous 3 days
- Previous treatment with tenecteplase
- Subjects > 80 years of age or < 18 years of age
- Cardiogenic shock
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis
- Hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients

WARNINGS AND SPECIAL PRECAUTIONS:

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.

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.

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

The concomitant use of unfractioned 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 mm Hg
- 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.

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.

Re-administration: See CONTRAINDICATIONS.

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.

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.

INTERACTIONS:
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.

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

HUMAN REPRODUCTION:
Pregnancy:
There is a limited amount of data from the use of METALYSE in pregnant women (see CONTRAINDICATIONS).
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.

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

DOSAGE AND DIRECTIONS FOR USE:
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

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

Incompatibilities:

- METALYSE is incompatible with dextrose solution.
- No other medicinal product should be added to the injection solution or infusion line.
- METALYSE may be administered in a pre-existing intravenous line, containing 0,9 % sodium chloride solution only. If a line is used, this line should be flushed after METALYSE injection for proper delivery.

METALYSE should not be mixed with other medicines, neither in the same infusion-vial nor the same venous line (not even with heparin).

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 WARNINGS AND SPECIAL PRECAUTIONS.

Instructions for use, handling and disposal:

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.

Ensure that the appropriate vial size is chosen according to the body weight of the patient (as per the table above).

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

2. Remove the flip-off cap from the vial and open the box of the vial adapter.

3. 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.

4. Add the METALYSE Solvent to the vial by pushing the syringe plunger down **slowly** to avoid foaming.

5. Reconstitute by swirling gently.

6. The reconstituted preparation is a colourless to slightly yellow, clear solution. Only clear solution without particles should be used.

7. Just before administration, invert the vial with the syringe still attached, so that the syringe is below the vial.

8. 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 DOSAGE AND DIRECTIONS FOR USE).

9. Disconnect the syringe from the vial adapter.

10. METALYSE is to be administered to the patient, intravenously over 5 to 10 seconds. **It should not be administered into a line containing dextrose**.

11. Any unused solution should be discarded.

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

SIDE EFFECTS:

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).

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.

Immune system disorders

Uncommon: anaphylactoid reaction (incl. 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)

Eye disorders

Very rare :	eye haemorrhage

Cardiac disorders:

Very common :	reperfusion dysrhythmias (such as asystole, accelerated idioventricular dysrhythmia, dysrhythmias, extrasystoles, atrial fibrillation, atrioventricular block first degree – atrioventricular block complete, bradycardia, tachycardia, ventricular dysrhythmias, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with METALYSE. Reperfusion dysrhythmia may lead to cardiac arrest, can be life-threatening and may require the use of conventional anti-dysrhythmic therapies.
Rare:	pericardial haemorrhage

Vascular disorders:

Very common:	haemorrhage
Uncommon:	embolism

Respiratory, thoracic and mediastinal disorders:

Common:	epistaxis
Uncommon:	pulmonary haemorrhage

Gastrointestinal disorders:

Common:	gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage), nausea, vomiting
Uncommon:	retroperitoneal haemorrhage (such as retroperitoneal haematoma)

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

Very common:	injection site haemorrhage, puncture site haemorrhage

Investigations

Very common:	decreased blood pressure
Common:	increased body temperature

Injury, poisoning and procedural complications:

Very rare:	fat embolism, which may lead to corresponding consequences in the organs concerned

Surgical and medical procedures:
Common: transfusion

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding, substitution therapy (plasma, platelets) may be considered. (Please refer to WARNINGS AND SPECIAL PRECAUTIONS.)
Further treatment is symptomatic and supportive.

IDENTIFICATION:
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.

PRESENTATION:
Each pack contains: A 20 mL glass vial containing a lyophilised cake for preparation of a solution for injection. The cake 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.

STORAGE INSTRUCTIONS:
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.

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 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.

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

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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	NS2

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