SECTION VIII

GUIDLINES FOR CLINICAL USE

INDICATIONS AND USAGE

Metalyse® is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST segment elevation or new onset left bundle branch block within six hours of symptom onset.

CONTRAINDICATIONS

The use of Metalyse® therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits.

Thrombolytic therapy is associated with a higher risk of bleeding.

Metalyse® is **contraindicated** in the following situations:

- Significant bleeding disorder either currently or within the past 6 months
- Patients currently undergoing concomitant oral anticoagulant therapy (INR >1.3)
- History of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (>2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis
- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

Metalyse® has the following **special warnings and precautions for use**:

Bleeding is the most common complication encountered during Metalyse® therapy. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Metalyse® therapy, bleeding from a recent puncture site may occur. Therefore, 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 Metalyse®.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding have been 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 1g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative.

The potential risks of Metalyse® use should be balanced with anticipated 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
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight <60 kg

Arrhythmias associated with reperfusion may result from coronary thrombolysis. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Metalyse® is administered.

GPIIb/IIIa antagonists: there is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration of Metalyse® is not recommended since at present there is no such experience. However, no antibody formation to the Metalyse® molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, Metalyse® should not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and α_2-antiplasmin.

Haemorrhage

Haemorrhage is a 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. Occasionally, (< 10%) gastrointestinal or genitourinary bleeding and epistaxis occurred. Haemopericardium, retroperitoneal bleedings and cerebral haemorrhage were rarely observed (< 1%). Blood transfusions were rarely required.

Cardiovascular events

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

- **Very common** (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- **Common** (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- **Uncommon** (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- **Rare** (>0.01%, <0.1%): pulmonary embolism

These cardiovascular events can be life threatening.

Metalyse® therapy may lead to crystal cholesterol embolisation or thrombotic embolism in very rare cases.

Anaphylactoid reactions

Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other

Nausea and/or vomiting and fever were commonly reported and are the most frequent of the remaining adverse events.

Re-administration

See above

Interactions

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 (e.g. ticlopidine, clopidogrel, low molecular weight heparin) may increase the risk of bleeding prior to, during or after Metalyse® therapy.

Pregnancy and lactation

No experience in pregnant women is available for Metalyse®. Because animal studies have shown a high risk of vaginal bleeding – presumably from the placenta – and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks that might aggravate an acute life-threatening situation.

It is not known if Metalyse® is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe bleeding, 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 1g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative.

In general, management of overdose should be discussed with the local haematology laboratory.

DOSAGE AND ADMINISTRATION

POSOLOGY AND METHOD OF ADMINISTRATION

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 soon as possible after onset of symptoms.

Metalyse® should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg). The volume required to administer the correct dose can be calculated from the following scheme.

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

A pre-existing intravenous line may be used for administration of Metalyse® in 0.9% sodium chloride solution only.

METALYSE® IS INCOMPATIBLE WITH DEXTROSE SOLUTION

No other medicinal product should be added to the injection solution.

Adjunctive therapy

Aspirin (acetylsalicylic acid) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

Aspirin should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The aspirin dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

Patients' body weight category (kg)	Metalyse® (U)	Metalyse® (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

Table 10. *Metalyse® dosing scheme*

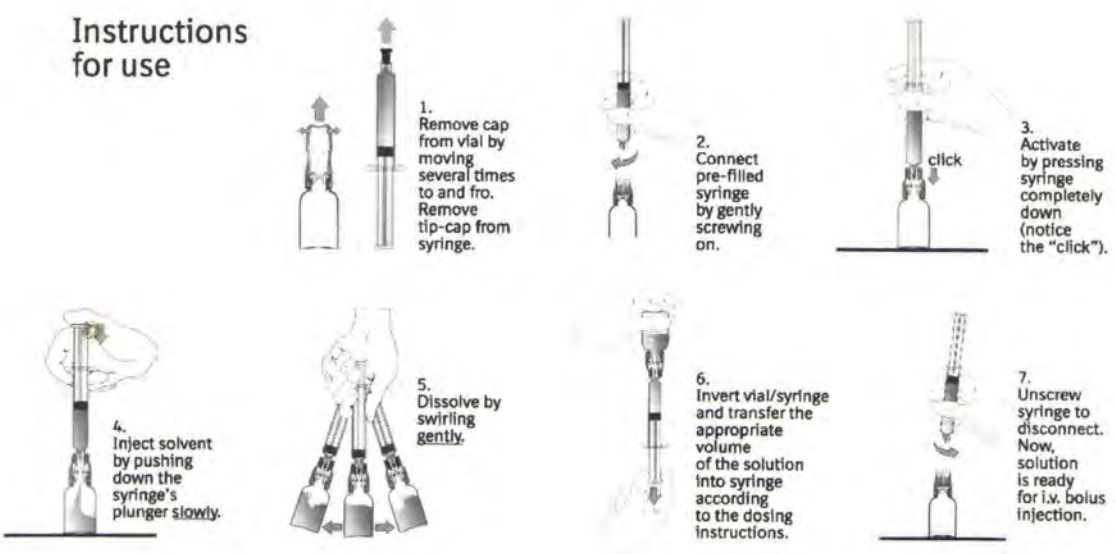
INSTRUCTIONS FOR HANDLING AND DISPOSAL

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.
2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Activate by pressing the connected syringe down until a click sound confirms that it is engaged.
5. Add the water for injections into the vial by pushing the syringe plunger down slowly to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation 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. Withdraw into the syringe the appropriate volume of reconstituted solution of Metalyse®, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Metalyse® is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

NATURE AND CONTENTS OF CONTAINER

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.

10 ml polypropylene syringe pre-filled with the appropriate volume of water for injections for reconstitution.



STABILITY AND STORAGE

Shelf life as packaged for sale

2 years

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for up to 24 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.

Special precautions for storage

Do not store above 30°C. Keep the container in the outer carton.