APPROVED PROFESSIONAL INFORMATION
ACTILYSE 50 mg and ACTILYSE SOLVENT

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ACTILYSE® 50 mg

powder for solution for injection/infusion

ACTILYSE® SOLVENT

solvent for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTILYSE 50 mg
One vial (50 mL) contains 50 mg alteplase (recombinant human tissue-type plasminogen activator) in 2 333 mg dry substance.

ACTILYSE Solvent
One vial of solvent contains 50 mL sterilised water for injection.

The reconstituted solution contains 1 mg alteplase per mL.
Sugar free.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

ACTILYSE 50 mg: One 50 mL vial containing 2 333 mg dry substance (a white to pale yellow cake).
ACTILYSE Solvent: One 50 mL vial containing a clear colourless liquid (sterilised water for injection).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fibrinolytic therapy in acute myocardial infarction for patients in whom treatment can be started within 6 hours of symptom onset.

Thrombolytic (fibrinolytic) treatment in patients with acute massive pulmonary embolism with haemodynamic instability. The diagnosis should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning.
There is no evidence for positive effects on mortality and late morbidity related to pulmonary embolism in haemodynamically stable patients.

Thrombolytic (fibrinolytic) treatment of acute ischaemic stroke.
Treatment must be started as early as possible, but within 4,5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage) (see section 4.3). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

4.2 Posology and method of administration

Posology

ACTILYSE should be given as soon as possible after symptom onset.

Myocardial Infarction
In patients with myocardial infarction, in whom treatment can be started within 6 hours after symptom onset, ACTILYSE should be administered according to the following dose regimen:

- 15 mg as an intravenous bolus,
- 50 mg as an infusion over the first 30 minutes, followed by an infusion of 35 mg over 60 minutes until the maximal dose of 100 mg.

In patients with a body weight below 65 kg the dose should be adjusted with:

- 15 mg as an intravenous bolus, and 0,75 mg/kg body weight over 30 minutes (maximum 50 mg), followed by an infusion of 0,5 mg/kg over 60 minutes (maximum 35 mg).

The total dose should not exceed 1,5 mg/kg in patients with a body weight below 65 kg.

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

Pulmonary Embolism
A total dose of 100 mg should be administered in two hours. The most experience available is with the following dose regimen:

- 10 mg as an intravenous bolus over 1 - 2 minutes,
- 90 mg as an intravenous infusion over 2 hours.

The total dose should not exceed 1,5 mg/kg in patients with a body weight below 65 kg.

Adjunctive therapy
After treatment with ACTILYSE, heparin therapy should be initiated (or resumed) when activated partial thromboplastin time (aPTT) values are less than twice the upper limit of normal. The infusion should be adjusted to maintain an activated partial thromboplastin time (aPTT) between 50 - 70 seconds (1,5 to 2,5 fold of the reference value).

Acute ischaemic stroke
Only to be used by doctors experienced in the treatment of ischaemic stroke.

The recommended total dose is 0,9 mg/kg body weight (maximum of 90 mg) starting with 10 % of the total dose administered as an initial intravenous bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes.

Treatment should be initiated as early as possible, but within 4,5 hours of symptom onset. The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Adjunctive therapy
The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid during the first 24 hours after the symptom-onset has not been investigated sufficiently. Therefore, administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with ACTILYSE. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10 000 IU per day, administered subcutaneously.

Method of administration
For reconstitution instructions prior to administration, see section 6.6.

For exact dosing, administration of ACTILYSE with perfusors/pumps is preferable; however, a drip infusion set can be used instead.

To provide the patient with the maximum benefit of ACTILYSE, residual volume remaining in the I.V. application devices should be kept to a minimum.

4.3 Contraindications
Hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients listed in section 6.1.

The following contraindications apply in general:

ACTILYSE should not be used in cases where there is a high risk of haemorrhage such as:

- Significant bleeding disorder at present or within the past 6 months or known haemorrhagic diathesis
- Patients receiving effective oral anticoagulant treatment, e.g. vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) (INR > 1,3) (see section 4.4, subsection "Bleeding")
- Any history of central nervous system damage, (i.e. neoplasm, aneurysm, intracranial or spinal surgery, ischaemic stroke in the past 3 months)
- History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
- Uncontrolled arterial hypertension, systolic BP ≥ 180 mm Hg, diastolic BP ≥ 110 mm Hg
- Major surgery, major biopsy, major fracture or significant trauma in the past 6 weeks (this includes any trauma associated with the current acute myocardial infarction), recent trauma to head or cranium
- Cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery within the past 10 days, recent puncture of a non-compressible blood vessel (e.g. subclavian and jugular vein puncture)
- Haemorrhagic stroke or stroke of unknown origin at any time
- Severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Infective endocarditis, pericarditis
- Acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices
- Arterial aneurisms, arterial/venous (A-V) malformations, dissecting aortic aneurism
- Intracranial neoplasm, known or suspected
- Neoplasm with increased bleeding risk

In the indications of acute myocardial infarction and pulmonary embolism the following additional contraindications apply:

- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 3 months, except current acute ischaemic stroke within 4,5 hours

In the indication acute ischaemic stroke the following contraindications apply in addition:

- Symptoms of ischaemic attack that began more than 4,5 hours prior to infusion start or when time of symptom onset is unknown
- Symptoms of acute ischaemic stroke that were either rapidly improving or minor before start of infusion
- Severe stroke as assessed clinically (e.g. National Institute of Health Stroke Scale (NIHSS) > 25) and/or by appropriate imaging techniques
- Seizure at the onset of stroke

- History of previous stroke or serious head-trauma within three months
- A combination of previous stroke and diabetes mellitus
- Administration of heparin within 48 hours preceding the onset of stroke with an elevated activated partial thromboplastin time (aPTT) at presentation
- Platelet count of less than 100 000/mm^3
- Systolic blood pressure > 180 or diastolic blood pressure > 110 mm Hg, or aggressive management (I.V. medication) necessary to reduce blood pressure to these limits
- Blood glucose < 2,78 or > 22,2 mmol/L

ACTILYSE is not indicated for the therapy of acute stroke in children and adolescents under 18 years or adults over 80 years of age.

4.4 Special warnings and precautions for use

ACTILYSE should be used by doctors experienced in the use of thrombolytic treatment and with the facilities to monitor that use. It is recommended that when ACTILYSE is administered, standard resuscitation equipment and medication 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.

Each patient being considered for therapy with ACTILYSE should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Hypersensitivity

No sustained antibody formation to the recombinant human tissue - type plasminogen activator molecule has been observed after treatment. There is no systematic experience with re-administration of ACTILYSE.

Immune-mediated hypersensitivity reactions associated with the administration of ACTILYSE can be caused by the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients (see also section 4.3 Contraindications).

There is also a risk of hypersensitivity reactions mediated through a non-immunological mechanism.

Angio-oedema represents the most common hypersensitivity reaction reported with ACTILYSE. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors (see Section 4.5 Interactions with Other

Medicines and Other Forms of Interactions). Patients treated for any authorised indication should be monitored for angio-oedema during and for up to 24 hours after infusion.

If a severe hypersensitivity reaction (e.g. angio-oedema) occurs, the infusion should be discontinued and appropriate treatment promptly initiated. This may include intubation.

A dose exceeding 100 mg of ACTILYSE (90 mg in acute ischaemic stroke) should not be given because it has been associated with an increase in intracranial bleeding.

Bleeding

The most common complication encountered during ACTILYSE therapy is bleeding. As fibrin is lysed during ACTILYSE therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cut down sites and needle puncture sites).

ACTILYSE is intended for administration by intravenous infusion only. Intramuscular injections and non-essential handling of the patient should be avoided during treatment with ACTILYSE. Venepunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTILYSE it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, in particular cerebral haemorrhage, the infusion of ACTILYSE and any concomitant heparin should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In patients who fail to respond to the 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 assessment after each administration. A target fibrinogen level of 1g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents should also be considered.

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

- Haemostatic defects including those secondary to severe hepatic or renal disease
- Recent intramuscular injection or recent traumas, such as biopsies, puncture of major vessels, cardiac massage for resuscitation

- Septic thrombophlebitis or occluded AV cannula at the seriously infected site
- Conditions with an increased risk of haemorrhage, which are not mentioned under section 4.3
- Patients receiving oral anticoagulant treatment:
  The use of ACTILYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.

For the treatment of acute myocardial infarction and acute pulmonary embolism the following special warnings and precautions apply in addition:

- Systolic blood pressure > 160 mm Hg
- Advanced age, which may increase the risk of intracerebral haemorrhage. As the therapeutic benefit is also increased in elderly patients, the risk-benefit evaluation should be carried out carefully.

For the treatment of acute myocardial infarction the following special warnings and precautions apply in addition:

Dysrhythmias

Coronary thrombolysis may result in dysrhythmias associated with reperfusion. These dysrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarisations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction. Reperfusion dysrthymias may lead to cardiac arrest, can be life threatening and may require the use of anti-dysrhythmic medicines. It is recommended that anti-dysrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTILYSE are administered.

Glycoprotein IIb/IIIa antagonists

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

Thrombo-embolism

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with left heart thrombus e.g. mitral stenosis or atrial fibrillation.

For the treatment of acute ischaemic stroke the following special warnings and precautions apply in addition:

Treatment must be performed under the supervision of a doctor trained and experienced in neurological care. For the verification of treatment indication, remote diagnostic measures may be considered as appropriate (see section 4.1, subsection “Thrombolytic (fibrinolytic) treatment of acute ischaemic stroke”).

Compared with other indications patients with acute ischaemic stroke treated with ACTILYSE have a markedly increased risk of intracranial haemorrhage as the bleeding

occurs predominantly into the infarcted area. This applies in particular in the following cases:

- All situations listed in section 4.3 and in general in all situations involving a high risk of haemorrhage
- Small asymptomatic aneurysms of the cerebral vessels
- Late time-to-treatment onset
- Patients pre-treated with acetylsalicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if ACTILYSE treatment is delayed. Not more than 0,9 mg alteplase/kg bodyweight (max. of 90 mg) should be administered in view of the increased risk of cerebral haemorrhage.

Treatment should not be initiated later than 4,5 hours after the onset of symptoms because of unfavourable benefit-risk ratio mainly based on the following:

- Positive treatment effects decrease over time
- Particularly in patients with prior ASA treatment the mortality rate increases
- Increased risk of symptomatic haemorrhage

Blood pressure (BP) monitoring during treatment administration and up to 24 hours is necessary; I.V. antihypertensive therapy is recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg.

The therapeutic benefit is reduced in patients who have had a prior stroke or in whom uncontrolled diabetes exists. The benefit-risk ratio is considered less favourable, although still positive in these patients.

In patients with very mild stroke, the risks outweigh the expected benefit and they should not be treated with ACTILYSE.

Patients with very severe stroke are at higher risk of intracerebral haemorrhage and death and should not be treated with ACTILYSE.

Patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death. In such patients, the benefit-risk ratio should be thoroughly considered.

In stroke patients the likelihood of a favourable outcome decreases with increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or relevant intracranial bleeding increases, independently of treatment. Patients over 80, patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 2,78 mmol/L or > 22,2 mmol/L at baseline should not be treated with ACTILYSE.

Reperfusion of the ischaemic area may induce cerebral oedema in the infarcted zone. Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with alteplase.

The use of rigid catheters should be avoided.

Paediatric population
As yet, there is only limited experience with the use of ACTILYSE in children.

4.5 Interaction with other medicines and other forms of interaction
No formal interaction studies with ACTILYSE and medicinal products commonly administered in patients with acute myocardial infarction have been performed.

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

Concomitant treatment with ACE inhibitors may enhance the risk of suffering a hypersensitivity reaction (see section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation
There is very limited experience with the use of ACTILYSE during pregnancy and lactation. It is not known whether alteplase is excreted into breast milk. Safety in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Side effects listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000); not known (cannot be estimated from the available data).

Indications - myocardial infarction, pulmonary embolism and acute ischaemic stroke
The most frequent adverse reaction associated with ACTILYSE is bleeding (common: major bleeds; very common: any haemorrhage) resulting in a fall in haematocrit and/or haemoglobin values. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.

The type of bleeds associated with thrombolytic therapy can be divided into two broad categories:

- Superficial bleeding, normally from punctures or damaged blood vessels
- Internal bleeding at any site or body cavity.

Intracranial haemorrhage may be associated with neurological symptoms such as somnolence, aphasia, hemiparesis and convulsions.

The number of patients treated in clinical trials in the indications pulmonary embolism and stroke (within the 0 – 4,5 hours time window) is very small in comparison to the number in the trial for myocardial infarction described above. Therefore, small numerical differences observed in comparison with the number in myocardial infarction were presumably attributable to the small sample size. Except for intracranial haemorrhage as a side effect in the indication stroke and reperfusion dysrhythmias in the indication myocardial infarction, there is no medical reason to assume that the qualitative and quantitative side effect profile of ACTILYSE in the indications pulmonary embolism and acute ischaemic stroke is different from the profile in the indication myocardial infarction.

Immune system disorders
Rare: Anaphylactoid reactions, which are usually mild, but can be life threatening. They may appear as

- rash
- urticaria
- bronchospasm
- angio-oedema
- hypotension
- shock or any other symptom associated with hypersensitivity

If they occur, conventional anti-allergic therapy should be initiated. In such cases a relatively larger proportion of patients were receiving concomitant angiotensin converting enzyme inhibitors. No definite anaphylactic (IgE mediated) reactions with ACTILYSE are known. Transient antibody formation with ACTILYSE has been observed in cases and with low titres, but a clinical relevance of this finding could not be established.

Eye disorders
Rare: eye haemorrhage

Cardiac disorders
Rare: pericardial haemorrhage

Vascular disorders
Very common: haemorrhage, such as haematoma
Rare: embolism (arterial, venous and both), which may lead to corresponding consequences in the organs concerned

Rare: bleeding of parenchymatous organs, such as
- hepatic haemorrhage
- pulmonary haemorrhage

Respiratory, thoracic and mediastinal disorders
Uncommon: respiratory tract haemorrhage, such as
- pharyngeal haemorrhage
- haemoptysis
- epistaxis

Gastrointestinal disorders
Gastrointestinal haemorrhage, such as
Common:
- gastric haemorrhage
- gastric ulcer haemorrhage
- rectal haemorrhage
- haematemesis
- melaena
- mouth haemorrhage

Uncommon: gingival bleeding
Rare:
- nausea
- 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
Common: injection site haemorrhage, puncture site haemorrhage, such as
- catheter site haematoma
- catheter site haemorrhage

Investigations
Uncommon: decreased blood pressure

Indication myocardial infarction
Cardiac disorders

Uncommon: reperfusion dysrhythmias, such as

- dysrhythmia
- extrasystoles
- atrial fibrillation
- atrioventricular block first degree to atrioventricular block complete
- bradycardia
- tachycardia
- ventricular dysrhythmia
- ventricular fibrillation
- ventricular tachycardia in close temporal relationship to treatment with ACTILYSE.

Reperfusion dysrhythmias may lead to cardiac arrest, can be life-threatening and may require the use of conventional anti-dysrhythmic therapies.

Indications - myocardial infarction and pulmonary embolism

Nervous system disorders

Common: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation stroke
- intracranial haematoma
- subarachnoid haemorrhage

Indication - acute ischaemic stroke

Nervous system disorders

Very Common: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation stroke
- intracranial haematoma
- subarachnoid haemorrhage

Symptomatic intracerebral haemorrhages represents the major adverse event (up to 10 % of patients). However, this had not shown an increased overall morbidity or mortality.

Post-marketing side effects

The following side effects were observed post-marketing therefore the frequencies are not known:

Investigations
Increased body temperature

Injury, poisoning and procedural complications
Fat embolism, which may lead to corresponding consequences in the organs concerned

Surgical and medical procedures
Transfusion

Gastrointestinal disorders
Vomiting
Nausea and vomiting can also occur as symptoms of myocardial infarction.

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
A reduction in fibrinogen and other blood coagulation components may occur after overdosage.
In most cases it is sufficient to await the physiological regeneration of these factors after the ACTILYSE therapy has been terminated. If however, severe bleeding results, the infusion of fresh frozen plasma or fresh blood is recommended and, if necessary, synthetic antifibrinolytics may be administered.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A 31 Enzymatic preparations

Mechanism of action
Alteplase is a glycoprotein, which activates plasminogen directly to plasmin. When administered intravenously, alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, induces the conversion of plasminogen to plasmin and thus leads to dissolution of the fibrin clot.

Pharmacodynamic effects
Due to its relative fibrin-specificity alteplase leads to a modest decrease of the circulating fibrinogen levels to about 60 % at 4 hours, which is generally reverted to more than 80 %

after 24 hours. Plasminogen and alpha-antiplasmin decrease to about 20 % and 35 % respectively after 4 hours and increase again to more than 80 % at 24 hours.
A marked and prolonged decrease of the circulating fibrinogen level is only seen in few patients.

5.2 Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 mL/min). The relevant plasma half-life $t_{½}$ alpha is 4 - 5 minutes. This means that after 20 minutes less than 10 % of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ACTILYSE 50 mg

L-arginine
Phosphoric acid
Polysorbate 80
Trace residue: gentamicin from manufacturing process.

ACTILYSE Solvent

Sterilised water for injection

6.2 Incompatibilities

The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/mL (0,9 %) solution for injection up to a minimal concentration of 0,2 mg/mL.

A further dilution of the 1 mg/mL reconstituted solution with sterilised water for injection or the use of carbohydrate infusion solutions, e.g. dextrose is not recommended due to increased turbidity of the reconstituted solution.

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

6.3 Shelf life

Unopened vials

3 years.

Reconstituted solution
The reconstituted solution may be stored in a refrigerator (2 - 8 °C) for up to 24 hours and for up to 8 hours at temperatures at or below 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.

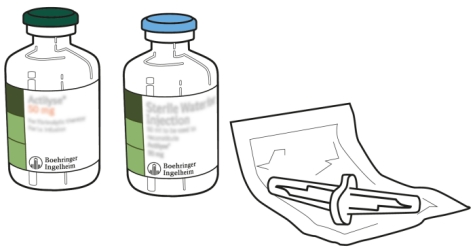
6.4 Special precautions for storage
Store at or below 30 °C.

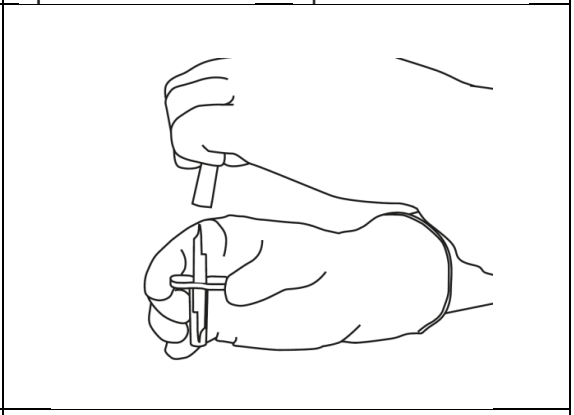
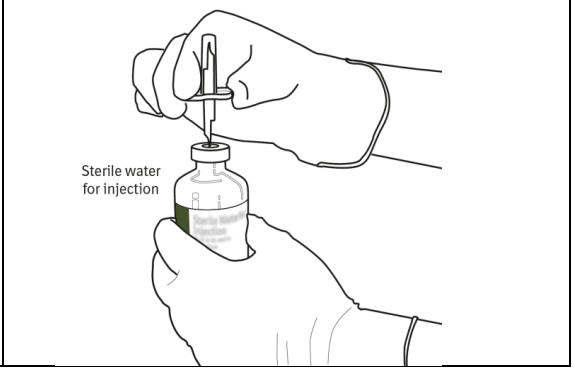
Protect the lyophilised substance from light.
ACTILYSE should be kept in the original carton until preparation.
The contents of the ACTILYSE package must not be used after the expiry date.
For storage conditions after reconstitution of the medicine, see section 6.3.

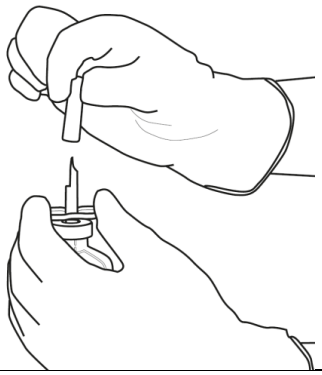
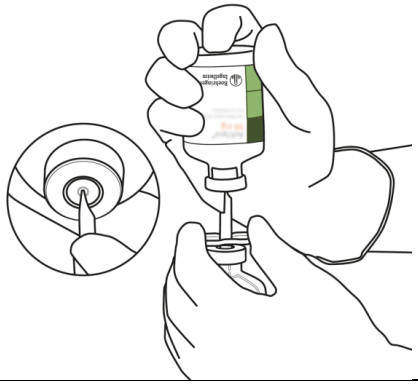
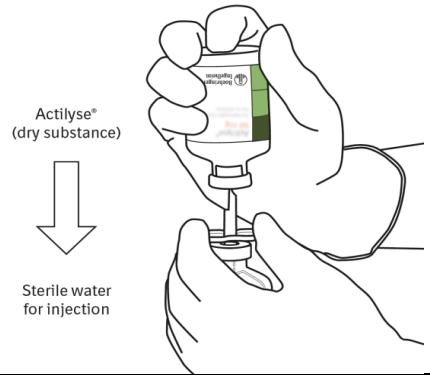
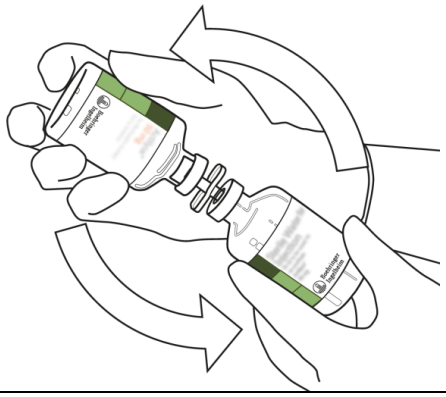
6.5 Nature and contents of container
One injection vial with dry substance and one vial with 50 mL solvent.
A transfer set (cannula) to be used during the reconstitution is also included in the pack - refer to section 6.6.

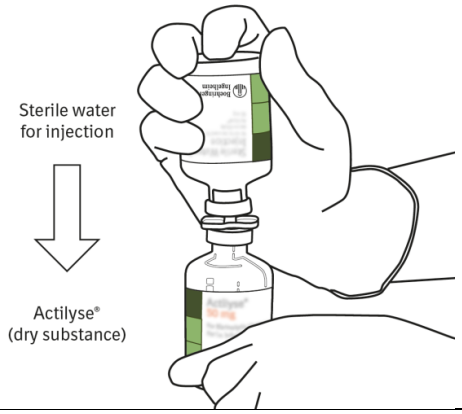
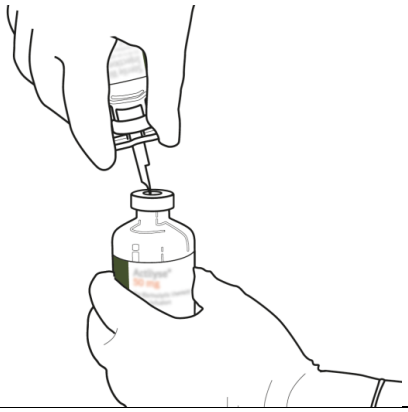
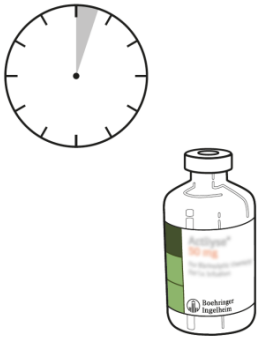
6.6 Special precautions for disposal and other handling
Directions for reconstitution
Under aseptic conditions the contents of an injection vial of ACTILYSE dry substance should be dissolved in sterile water for injection to a concentration of 1 mg ACTILYSE per mL and administered intravenously. Thus, for reconstitution to the final concentration of 1 mg alteplase/mL the full volume of solvent provided should be transferred to the vial containing the ACTILYSE dry substance. Use only the vial of sterile water for injection provided in the pack for reconstitution.

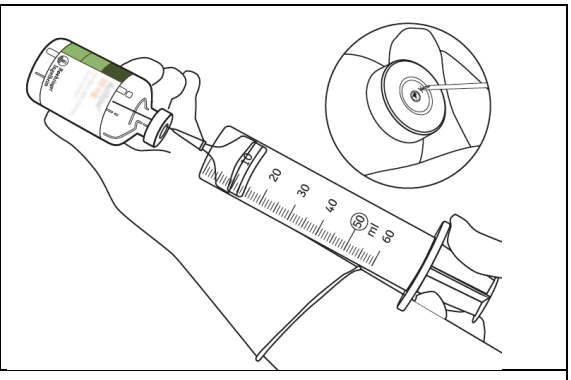
Instructions for reconstituting ACTILYSE

1.	Reconstitute immediately before administration.	

2.	Remove the protective cap on the two vials containing the sterile water and ACTILYSE dry substance by flipping them up with a thumb.	
3.	Swab the rubber top of each vial with an alcohol wipe.	
4.	Remove the transfer cannula from its cover. Do not disinfect or sterilize the transfer cannula; it is sterile. Take one cap off.	
5.	Stand the sterile water vial upright on a stable surface. From directly above, puncture the rubber stopper vertically in the stopper center with the transfer cannula, by pressing gently but firmly, without twisting.	

6.	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Remove the remaining cap on top of the transfer cannula.	
7.	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Hold the vial with ACTILYSE dry substance above the transfer cannula and position the tip of the transfer cannula right in the center of the stopper.	
	Push down the vial with the dry substance onto the transfer cannula from directly above, puncturing the rubber stopper vertically and gently but firmly without twisting.	
8.	Invert the two vials and allow the water to drain completely into the dry substance.	

		
9.	Remove the empty water vial together with the transfer cannula. They can be disposed of.	
10.	Take the vial with reconstituted ACTILYSE and swirl gently to dissolve any remaining powder, but do not shake, as this will produce foam.	
	If there are bubbles, let the solution stand undisturbed for a few minutes to allow them to disappear.	
11.	The solution consists of 1 mg/mL ACTILYSE. It should be clear and colourless to pale yellow and it should not contain any particles.	

12.	Remove the amount required using a needle and a syringe. Do not use the puncture location from the transfer cannula to avoid leakage.	
13.	Use immediately. Dispose of any unused solution.	

The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/mL (0,9 %) solution for injection up to a minimal concentration of 0,2 mg/mL.

A further dilution of the 1 mg/mL reconstituted solution with sterilised water for injection or the use of carbohydrate infusion solutions, e.g. dextrose is not recommended due to increased turbidity of the reconstituted solution.

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

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

ACTILYSE 50 mg: U/31/229
ACTILYSE Solvent: U/32.4/230

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 22 December 1988

10. DATE OF REVISION OF THE TEXT

17 May 2022

BOTSWANA Reg. No. ACTILYSE 50 mg powder for infusion ACTILYSE solvent	 B9304880 B9304885	 S2 S3
NAMIBIA Reg. No. ACTILYSE 50 mg powder for infusion ACTILYSE solvent	 90/31/00450 90/32.4/00451	 NS2 NS2

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