PROFESSIONAL INFORMATION

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 (AMI) for patients in whom treatment can be started within 6 hours of symptom onset.

Thrombolytic (fibrinolytic) treatment in patients with acute massive pulmonary embolism (PE) 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 (AIS) within 4,5 hours from last known well and after exclusion of intracranial haemorrhage.

4.2 Posology and method of administration

Posology

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

Acute myocardial infarction (AMI)

In patients with acute myocardial infarction, in whom treatment can be started within 6 hours after symptom onset, ACTILYSE should be administered according to the following dose regimen in patients with a body weight ≥ 65 kg:

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

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

- 15 mg as an intravenous bolus, immediately followed by

- 0,75 mg/kg body weight as an intravenous infusion over the first 30 minutes (maximum 50 mg), immediately followed by an intravenous infusion of 0,5 mg/kg over 60 minutes (up to a maximum of 35 mg).

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

Adjunctive therapy - AMI

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

Acute massive pulmonary embolism (PE)

In patients with a body weight ≥ 65 kg:

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, immediately followed by
- 90 mg as an intravenous infusion over 2 hours until the maximum total dose of 100 mg.

In patients with a body weight < 65 kg:

- 10 mg as an intravenous bolus over 1 - 2 minutes, immediately followed by
- an intravenous infusion over 2 hours up to a maximum total dose of 1,5 mg/kg body weight

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

Adjunctive therapy - PE

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 (AIS)

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 for adults and children ≥ 16 years of age (see sections 4.3 and 4.4) as early as possible and no later than 4,5 hours after last known well and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Dosing table for acute ischaemic stroke

Weight (kg)	Total Dose (mg)	Bolus Dose (mg)	Infusion Dose[a] (mg)
40	36,0	3,6	32,4
42	37,8	3,8	34,0
44	39,6	4,0	35,6
46	41,4	4,1	37,3
48	43,2	4,3	38,9
50	45,0	4,5	40,5
52	46,8	4,7	42,1
54	48,6	4,9	43,7
56	50,4	5,0	45,4
58	52,2	5,2	47,0
60	54,0	5,4	48,6
62	55,8	5,6	50,2
64	57,6	5,8	51,8
66	59,4	5,9	53,5
68	61,2	6,1	55,1
70	63,0	6,3	56,7
72	64,8	6,5	58,3
74	66,6	6,7	59,9

Weight (kg)	Total Dose (mg)	Bolus Dose (mg)	Infusion Dose[a] (mg)
76	68,4	6,8	61,6
78	70,2	7,0	63,2
80	72,0	7,2	64,8
82	73,8	7,4	66,4
84	75,6	7,6	68,0
86	77,4	7,7	69,7
88	79,2	7,9	71,3
90	81,0	8,1	72,9
92	82,8	8,3	74,5
94	84,6	8,5	76,1
96	86,4	8,6	77,8
98	88,2	8,8	79,4
100+	90,0	9,0	81,0

[a] given in a concentration of 1 mg/mL over 60 min.

Adjunctive therapy - AIS

The safety and efficacy of this regimen with concomitant administration of heparin or platelet aggregation inhibitors such as acetylsalicylic acid during the first 24 hours after treatment with ACTILYSE has not been investigated sufficiently. Therefore, administration

of intravenous heparin or platelet aggregation inhibitors such as acetylsalicylic acid should be avoided in the first 24 hours after treatment with ACTILYSE due to an increased haemorrhagic risk.

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.

Thrombectomy - AIS

Patients eligible for intravenous ACTILYSE should receive intravenous ACTILYSE even if mechanical thrombectomy is being considered.

Paediatric population

There is limited experience with the use of ACTILYSE in children and adolescents. Actilyse is contraindicated for the treatment of acute ischaemic stroke in children and adolescents under 16 years of age (see section 4.3). The dose for adolescents 16-17 years old is the same as for adults (see section 4.4 for recommendations on prior imaging techniques to be used).

Method of administration

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

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

The following contraindications apply in general:

Hypersensitivity to the active substance alteplase or any of the excipients listed in section 6.1.

ACTILYSE should not be used in situations associated with risk of bleeding such as:

- Significant bleeding disorder at present or within the past 6 months or known haemorrhagic diathesis
- Any history of central nervous system damage, (i.e. neoplasm, aneurysm, intracranial or spinal surgery, ischaemic stroke in the past 3 months)
- Uncontrolled arterial hypertension, systolic BP ≥ 180 mmHg, diastolic BP ≥ 110 mmHg (see section 4.4)

- 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
- 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
- Active ulcerative gastrointestinal disease, oesophageal varices
- Known arterial aneurisms and/or arterial/venous (A-V) malformation, dissecting aortic aneurism
- Intracranial neoplasm, known or suspected
- Neoplasm with increased bleeding risk

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

Situations associated with a risk of bleeding such as:

- Patients receiving effective oral anticoagulant treatment, e.g. vitamin K antagonists with INR > 1,3 and direct oral anticoagulants (DOACs) (see section 4.4, subsection "Bleeding")

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

Situations associated with a risk of bleeding such as:

- 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
- Patients receiving effective oral anticoagulant treatment, e.g. vitamin K antagonists with INR > 1,7 and direct oral anticoagulants (DOACs) (see section 4.4, subsection "Bleeding")
- 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
- History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
- History of serious head-trauma within three months

Use in children and adolescents

ACTILYSE is not indicated for the treatment of acute ischaemic stroke in children under 16 years of age (for adolescents ≥ 16 years of age see section 4.4).

4.4 Special warnings and precautions for use

ACTILYSE should be prescribed by doctors experienced in the use of thrombolytic treatment and with the facilities to monitor that use. This does not preclude the pre-hospital use of ACTILYSE. It is recommended that when ACTILYSE is administered, standard resuscitation equipment and medication be available in all circumstances.

Acute Ischaemic Stroke (AIS)

Treatment must be performed under the responsibility of doctors trained and experienced in neurovascular care. For the indication verification remote diagnostic measures may be considered as appropriate (see section 4.2; subsection “Acute ischaemic stroke (AIS)”).

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.

Bleeding

The most common complication encountered during ACTILYSE therapy is bleeding (see also section 4.3; for AIS see also section 4.2 adjunctive therapy). The concomitant use of other active substances affecting coagulation or platelet function may contribute to 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.

The use of rigid catheters should be avoided.

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.

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.

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
- Septic thrombophlebitis or occluded AV cannula at the seriously infected site

- 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
- Prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage
- History of previous stroke or transient ischaemic attack (TIA)

AMI and PE

- Systolic blood pressure > 160 mmHg, see also section 4.3
- Advanced age, i.e. patients 75 years or older, which may increase the risk of intracerebral haemorrhage
- Body weight < 50 kg

AIS

Intracerebral haemorrhages represents the most frequent adverse event. However, this had not shown an increased overall morbidity or mortality.

Compared with other indications patients with acute ischaemic stroke treated with ACTILYSE have a significantly 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
- Late time-to-treatment onset
- Patients pre-treated with acetylsalicylic acid (ASA) may have a greater risk of intracerebral haemorrhage and/or mortality, particularly if ACTILYSE treatment is delayed.
- Compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment. They are also more likely to have more severe strokes which are associated with a higher absolute risk of intracerebral haemorrhage when thrombolysed compared with milder strokes when thrombolysed or with non-thrombolysed patients. Although available data indicate that the net benefit of ACTILYSE in patients over 80 years is smaller compared with younger patients, ACTILYSE can be used in patients over 80 years on an individual benefit-risk basis. Patients of advanced age should be selected very carefully taking into account both the general health and the neurological status.

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 or any of the excipients (see also section 4.3).

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). Patients treated with ACTILYSE 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.

Thrombo-embolism

The use of ACTILYSE can increase the risk of thrombo-embolic events in patients with existing thrombi, e.g. left heart thrombus (mitral stenosis or atrial fibrillation, etc.).

Dysrhythmias - AMI

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 dysrhythmias 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 receptor antagonists - AMI

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

Blood pressure monitoring - AIS

To initiate thrombolysis, uncontrolled hypertension or systolic blood pressure > 185 mmHg or diastolic BP > 110 mmHg should be carefully managed.

Blood pressure (BP) monitoring during the first 24 hours is necessary; intravenous antihypertensive therapy is recommended if systolic BP > 180 mmHg or diastolic BP > 105 mmHg.

Special patient groups at reduced benefit-risk - AIS

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

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.

The benefit/risk ratio of ACTILYSE administration should be thoroughly considered in AIS patients with the following conditions:

- Seizure at the onset of stroke
- Blood glucose < 50 mg/dL or > 400 mg/dL (< 2,8 or > 22,2 mmol/L), which must be corrected before treatment initiation

Cerebral oedema - AIS

Reperfusion of the ischaemic area may induce cerebral oedema in the infarcted zone.

Paediatric population - AIS

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

When Actilyse is considered for the treatment of acute ischaemic stroke in carefully selected adolescents ≥ 16 years of age the benefit should be weighed carefully against the

risks on an individual basis and discussed with the patient and parent/guardian as appropriate. Adolescents ≥ 16 years of age should be treated according to the instruction in the label for the adult population after imaging by appropriate techniques to rule out stroke mimics and confirming arterial occlusion corresponding to the neurological deficit.

ACTILYSE contains polysorbate 80

This medicine contains 5,0 mg of polysorbate 80 in each 50 mg vial. Polysorbates may cause allergic reactions.

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 AMI, PE or AIS have been performed.

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 ACTILYSE therapy, see section 4.3.

AIS

Such medicinal products should be avoided in the first 24 hours after ACTILYSE treatment for acute ischaemic stroke.

ACE inhibitors

Concomitant treatment with ACE inhibitors may enhance the risk of experiencing a hypersensitivity reaction (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

There is very limited experience with the use of ACTILYSE during pregnancy.

Nonclinical studies performed with alteplase in doses higher than human doses exhibited foetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the medicine. Alteplase is not considered to be teratogenic.

In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.

Lactation

It is not known whether alteplase is excreted into breast milk.

Caution should be exercised when ACTILYSE 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 ACTILYSE.

Fertility

Clinical data on fertility are not available for ACTILYSE. Nonclinical studies performed with alteplase showed no adverse effect on fertility.

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

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

Respiratory, thoracic and mediastinal disorders

Respiratory tract haemorrhage, such as

Common: pharyngeal haemorrhage

Uncommon: haemoptysis, epistaxis

Rare: pulmonary haemorrhage

Gastrointestinal disorders

Gastrointestinal haemorrhage, such as

Common:

- gastric haemorrhage
- gastric ulcer haemorrhage
- rectal haemorrhage
- haematemesis
- melaena
- mouth haemorrhage
- 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 acute 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.

Indications – acute myocardial infarction and acute massive 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

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.

Vascular disorders

Bleeding of parenchymatous organs, such as hepatic haemorrhage

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 Overdose

Symptoms

If the maximum recommended dose is exceeded the risk of intracranial bleeding increases. A clinically significant reduction in fibrinogen and other blood coagulation components may occur after overdosage.

Therapy

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). Under physiological conditions, the major portion of alteplase in the circulation is inhibitor-bound. Hepatic clearance of alteplase is not hindered by the presence of other proteins including alteplase inhibitors. Complexes of alteplase and its inhibitor are eliminated as free alteplase. 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

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 since the occurrence of turbidity of the reconstituted solution cannot be excluded.

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

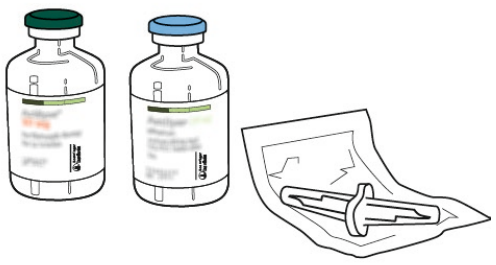
A transfer set (cannula) to be used during the reconstitution is also included in the pack - refer to section 6.6.

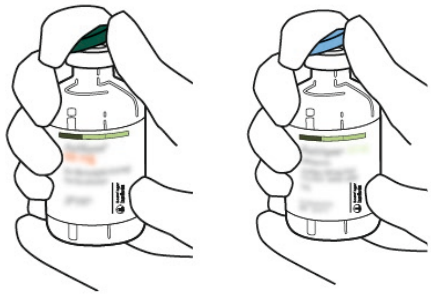
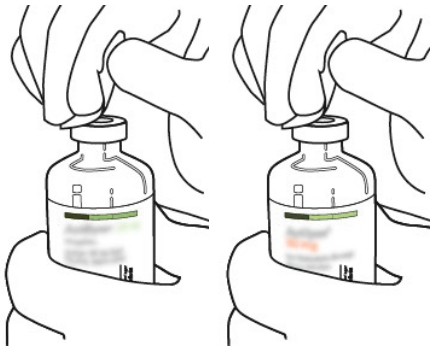
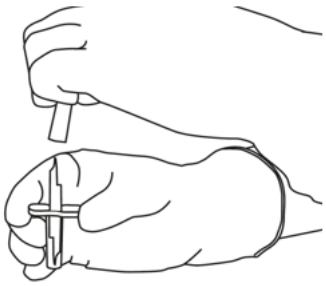
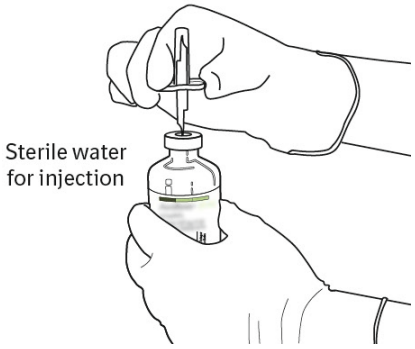
6.6 Special precautions for disposal and other handling

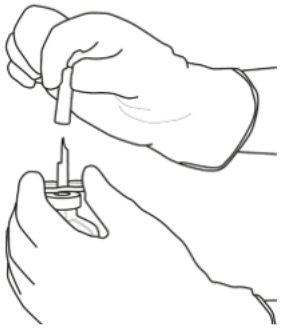
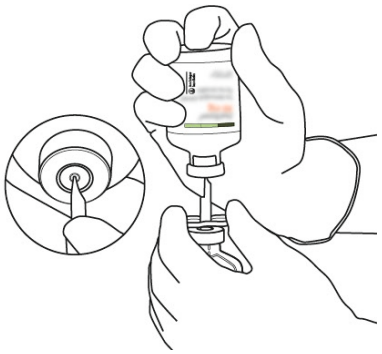
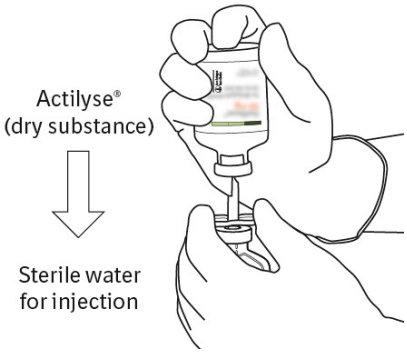
Directions for reconstitution

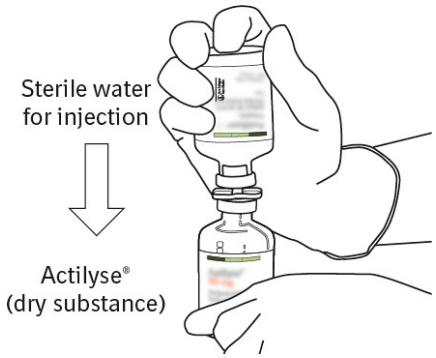
Under aseptic conditions the contents of an injection vial of ACTILYSE dry substance should be dissolved in sterile water for injection to a concentration of 1 mg ACTILYSE per mL and administered intravenously. Thus, for reconstitution to the final concentration of 1 mg alteplase/mL the full volume of 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.

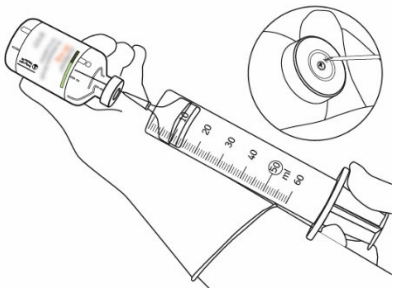
Instructions for reconstituting ACTILYSE

1.	Reconstitute immediately before administration.	

2.	Remove the protective cap on the two vials containing the sterile water and [Local Trade Name] 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 centre 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 [Local Trade Name] dry substance vertically above the transfer cannula and position the tip of the transfer cannula right in the centre 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 [Local Trade Name] 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 reconstituted solution consists of 1mg/mL [Local Trade Name]. It should be clear and colourless to pale yellow and it should not contain any particles.	

12.	Remove the amount required only by 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 since the occurrence of turbidity of the reconstituted solution cannot be excluded.

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

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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

06 October 2026

BOTSWANA Reg. No. ACTILYSE 50 mg powder for infusion ACTILYSE solvent	BOT2500007	S2
NAMIBIA Reg. No. ACTILYSE 50 mg powder for infusion ACTILYSE solvent	 90/31/00450 90/32.4/00451	 NS2 NS1