

# New Zealand Datasheet

## Name of Medicine

ACTILYSE®

Alteplase (recombinant human tissue-type plasminogen activator: rt-PA)

## Presentation

ACTILYSE 10 mg: clear glass injection vial containing 10 mg alteplase in 466.6 mg dry substance and 10 mL vial of sterilised water for injection.

ACTILYSE 20 mg: clear glass injection vial containing 20 mg alteplase in 933.2 mg dry substance and 20 mL vial of sterilised water for injection. (Not marketed)

ACTILYSE 50 mg: clear glass injection vial containing 50 mg alteplase in 2333 mg dry substance and 50 mL vial of sterilised water for injection.

## Uses

### Actions

The active ingredient of ACTILYSE is alteplase, a recombinant human tissue-type plasminogen activator, 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, inducing the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

Due to its relative fibrin-specificity, alteplase at a dose of 100 mg 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-2-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.

### Acute Myocardial Infarction (AMI) patients

Two ACTILYSE dose regimens have been studied in patients experiencing acute myocardial infarction. The comparative efficacy of these two regimens has not been evaluated.

#### Accelerated infusion in AMI patients

Accelerated infusion of ACTILYSE was studied in an international, multi-center trial (GUSTO) that randomized 41,021 patients with acute myocardial infarction to four thrombolytic regimens. Administration of 100 mg ACTILYSE over 90 minutes, with concomitant i.v. heparin infusion, led to a lower mortality after 30 days (6.3%) as compared to the administration of streptokinase, 1.5 million IU over 60 minutes, with s.c. or i.v. heparin (7.3%). The 1% absolute decrease in 30-day mortality for ACTILYSE compared to streptokinase was statistically significant ( $p = 0.007$ ). ACTILYSE-treated patients showed higher infarct related vessel patency rates at 60 and 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer.

A large scale mortality trial (ASSENT 2) in approx. 17,000 patients showed that alteplase and tenecteplase are therapeutically equivalent in reducing mortality (6.2% for both treatments, at 30 days). The use of tenecteplase was associated with a significantly lower incidence of non-intracranial bleedings compared to alteplase (26.4% versus 28.9%,  $p = 0.0003$ ). The reduction of the risk of bleeding is likely to be related to the increased fibrin specificity of tenecteplase and to its weight adapted regimen.

#### 3-hour infusion in AMI patients

In a double-blind, randomized trial (5013 patients) comparing ACTILYSE to placebo (ASSET study) patients infused with ACTILYSE within 5 hours of the onset of symptoms of acute myocardial infarction experienced improved 30-day survival compared to those treated with placebo. At 1 month, the overall mortality rates were 7.2% for the ACTILYSE-treated group and 9.8% for the placebo-treated group ( $p = 0.001$ ). This benefit was maintained at 6 months for ACTILYSE-treated patients (10.4%) compared to those treated with placebo (13.1%,  $p = 0.008$ ).

In a double-blind, randomized trial (721 patients) comparing ACTILYSE to placebo, patients infused with ACTILYSE within 5 hours of the onset of symptoms experienced improved ventricular function 10 - 22 days after treatment compared to the placebo group, when global ejection fraction was measured by contrast ventriculography (50.7% versus 48.5%,  $p = 0.01$ ). Patients treated with ACTILYSE had a 19% reduction in infarct size, as measured by cumulative release of HBD ( $\alpha$ -hydroxybutyrate dehydrogenase) activity compared to placebo-treated patients ( $p = 0.001$ ). Patients treated with ACTILYSE had significantly fewer episodes of cardiogenic shock ( $p = 0.02$ ), ventricular fibrillation ( $p < 0.04$ ) and pericarditis ( $p = 0.01$ ) compared to patients treated with placebo. Mortality at 21 days in ACTILYSE-treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients (1-sided  $p = 0.05$ ). Although these data do not demonstrate unequivocally a significant reduction in mortality for this study, they do indicate a trend that is supported by the results of the ASSET study.

In a placebo controlled trial (LATE) in 5711 AMI patients with onset of symptoms between 6 and 24 hours a 100 mg ACTILYSE over 3 hours infusion was compared with placebo. A non significant reduction of 14.1% (95% CI 0 - 28.1%,  $p > 0.05$ ) in 30-day-mortality was observed with ACTILYSE. In a pre-specified survival analysis in patients treated within 12 hours of symptom onset, a significant 25.6% reduction in mortality in favour of ACTILYSE (95% CI 6.3 - 45%;  $p = 0.023$ ) was observed.

### **Pulmonary embolism patients**

In a comparative randomized trial of alteplase versus urokinase in 63 patients with angiographically documented acute massive pulmonary embolism both treatment groups experienced a significant reduction in pulmonary embolism-induced pulmonary hypertension. Pulmonary haemodynamics improved significantly faster with ACTILYSE than with urokinase.

### **Acute ischaemic stroke patients**

Several studies have been carried out in the field of acute ischaemic stroke. The NINDS study is the only study without an upper age limit, i.e. which also included patients over 80 years. All other randomized trials have excluded patients over 80 years of age. Therefore, treatment decisions in this patient group require particular care on an individual patient basis.

Two placebo-controlled, double-blind trials (NINDS t-PA Stroke Trial, Part 1 and Part 2) enrolled patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerized tomography (CT) scan was performed prior to treatment to rule out the presence of symptomatic intracranial haemorrhage (SICH). Patients were also excluded for the presence of conditions related to risks of bleeding, for minor neurological deficit, for rapidly improving symptoms prior to initiating study treatment, or for blood glucose of  $< 50$  mg/dL or  $> 400$  mg/dL. Patients were randomized to receive either 0.9 mg/kg ACTILYSE (maximum of 90 mg), or placebo. ACTILYSE was administered as a 10% initial bolus over 1 minute followed by continuous intravenous infusion of the remainder over 60 minutes.

The initial study (NINDS-Part 1,  $n = 291$ ) evaluated neurological improvement at 24 hours after stroke onset. The primary endpoint, the proportion of patients with a 4 or more point improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery (NIHSS score = 0), was not significantly different between treatment groups. A secondary analysis suggested improved 3-months outcome associated with ACTILYSE treatment using the following stroke assessment scales: Barthel Index, Modified Rankin Scale (mRS), Glasgow Outcome Scale, and the NIHSS. A second study (NINDS-Part 2,  $n = 333$ ) assessed clinical outcome at 3 months as the primary outcome. A favourable outcome was defined as minimal or no disability using the four

stroke assessment scales: Barthel Index (score > 95), Modified Rankin Scale (score < 1), Glasgow Outcome Scale (score = 1), and NIHSS (score < 1). The odds ratio for favourable outcome in the ACTILYSE group was 1.7 (95% CI; 1.2 - 2.6). Compared to placebo there was 13% absolute increase in the number of patients with minimal or no disability (mRS 0 - 1) (OR 1.7; 95% CI 1.1 - 2.6). There was also a consistent benefit seen with ACTILYSE on other neurologic and disability scales. Secondary analyses demonstrated consistent functional and neurological improvement within all four stroke scales as indicated by median scores. These results were highly consistent with the 3-months outcome treatment effects observed in the Part 1 study. The incidences of all-cause 90-day mortality, SICH, and new ischemic stroke following ACTILYSE treatment compared to placebo indicated a significant increase in symptomatic SICH (according to NINDS definition) following ACTILYSE treatment within 36 hours (ACTILYSE 6.4%; Placebo 0.65%). In ACTILYSE-treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability (ACTILYSE 20.5%; Placebo 17.3%).

A pooled analysis of 2775 patients from 6 major randomized clinical trials (NINDS part 1 and 2, two ECASS trial and ATLANTIS part A and B) evaluated the disability status of patients treated with ACTILYSE or placebo. In this analysis, the odds of a favourable outcome at 3 months increased as the time to treatment with ACTILYSE decreased. A SICH rate was seen in 5.9% of patients treated with ACTILYSE versus 1.1% of controls ( $p < 0.0001$ ) which was associated with age but not with time to treatment. This analysis strongly confirms that rapid treatment with ACTILYSE is associated with better outcomes at 3 months. It also provides evidence that the therapeutic window may extend as far out as 4.5 hours.

In a large observational study (SITS-MOST: The Safe Implementation of Thrombolysis in Stroke-Monitoring Study) the safety and efficacy of ACTILYSE for acute stroke treatment within 3 hours in a routine clinical setting was assessed and compared with results from randomised clinical trials (RCTs). All patients had to be compliant with the European summary of the product characteristics of ACTILYSE. Treatment and outcome data of 6483 patients from 285 centres in 14 European countries were collected. Primary outcome were symptomatic intracranial haemorrhage within 24 hours and mortality at 3 months. The rate of SICH found in SITS-MOST was comparable with the SICH rate as reported in randomized trials 7.3% (95% CI 6.7 - 8.0) in SITS-MOST versus 8.6% (95% CI 6.1 - 11.1) in RCTs. Mortality was 11.3% (95% CI 10.5 - 12.1) in SITS-MOST versus 17% (95% CI 13.9 - 20.7) in RCTs. The results of SITS-MOST indicate that, the routine clinical use of ACTILYSE within 3 hours of stroke onset is as safe as reported in randomized clinical trials.

The ECASS III trial as a placebo-controlled, double-blind trial conducted in patients with acute stroke in a time-window of 3 - to 4.5 hours. The study enrolled patients with measurable neurological deficit compliant with the European summary of product characteristics (SPC) except the time-window. After exclusion of brain haemorrhage or major infarction by computed tomography, patients with acute ischemic stroke were randomized in a 1:1 double-blind fashion to intravenous alteplase (0.9 mg/kg bodyweight) or placebo. The primary end point was disability at 90 days, dichotomized for favourable (modified Rankin scale [mRS] 0 to 1) or unfavourable (mRS 2 to 6) outcome. The principal secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included mortality, SICH, and serious adverse events. A total of 821 patients were (418 alteplase/403 placebo) randomized. More patients achieved favourable outcome with alteplase (52.4%) versus placebo (45.2%; odds ratio [OR], 1.34; 95% CI 1.02 - 1.76;  $p = 0.038$ ). On the global analysis, outcome was also improved (OR, 1.28; 95% CI 1.00 - 1.65;  $p = 0.048$ ). The incidence of SICH was higher with alteplase versus placebo (any SICH 27.0% versus 17.6%,  $p = 0.0012$ ; SICH by NINDS definition 7.9% versus 3.5%,  $p = 0.006$ ). Mortality was low and not significantly different between alteplase (7.7%) and placebo (8.4%;  $p = 0.681$ ). The results of ECASS III show that ACTILYSE between 3 and 4.5 hours after symptom onset significantly improves clinical outcomes in patients with acute ischemic stroke.

The safety and efficacy of ACTILYSE for acute ischaemic stroke treatment up to 4.5 hours time onset to treatment (OTT) has been assessed by an ongoing AIS registry (SITS-ISTR: The Safe Implementation of Thrombolysis in Stroke registry). Primary outcome and mortality data of 15,294 patients in the 0 to 3 hours time window were compared with data from 947 patients treated between 3 to 4.5 hours after onset of AIS. At 3 months the incidence of symptomatic

intracerebral haemorrhage (according to the NINDS definition) was found to be slightly higher in the 3 to 4.5 hours time window (9.13%; 95% CI 7.38 - 11.24) as compared with the up to 3 hours time window (7.49% CI 7.07 - 7.93). Mortality rates were similar comparing the 3 to 4.5 hours time window (12.4%) with the 0 to 3 hours time window 12.3%.

## Pharmacokinetics

Alteplase is cleared rapidly from circulating blood. The organ primarily responsible for clearance is the liver (plasma clearance 550-680 mL/min). The level of alteplase present in plasma falls to 50% of the initial level within 5 minutes, to approximately 20% after 10 minutes and to less than 10% after 20 minutes (plasma half-life  $t_{1/2\alpha}$  is 4 – 5 min). For the residual amount remaining in a deep compartment, a  $\beta$  half-life of about 40 minutes has been measured.

When ACTILYSE is administered for restoration of dysfunctional central venous access devices according to the instructions circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations. If a 2 mg dose of alteplase was administered by bolus injection directly into the systemic circulation (rather than instilled into the catheter), the concentration of circulating alteplase would be expected to return to undetectable limits within 30 - 60 minutes.

## Indications

### *Myocardial Infarction*

ACTILYSE is indicated for fibrinolytic therapy in acute thrombotic artery occlusion to restore coronary artery patency, reduce infarct size, preserve ventricular function, prevent cardiac insufficiency and reduce mortality.

- 90 minutes (accelerated) dose regimen (see Dosage and administration): for patients in whom treatment can be started within 6 h of symptom onset;
- 3 hour dose regimen (see Dosage and administration): for patients in whom treatment can be started between 6 - 12 hrs after symptom onset.

### *Pulmonary Embolism*

ACTILYSE is also indicated in patients with acute massive pulmonary embolism accompanied by haemodynamic instability.

### *Acute Ischaemic Stroke*

ACTILYSE is indicated for thrombolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible 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). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

## Dosage and Administration

### Myocardial Infarction

ACTILYSE should be administered as soon as possible after the onset of symptoms. A total dose of 100 mg should not be exceeded.

- a) Accelerated (90 minute) dose regimen for patients in whom treatment can be started within 6 hours of symptom onset.
- 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 maximum dose of 100 mg has been administered.

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

- 15 mg as an intravenous bolus
- 0.75 mg/kg bodyweight over 30 minutes (maximum 50 mg) followed by an infusion of 0.5 mg/kg over 60 minutes (maximum 35 mg)

- b) 3 hour dosage regimen for patients in whom treatment can be started between 6 – 12 hours after symptom onset:-
- 10 mg as an intravenous bolus over 1 – 2 minutes
  - 50 mg as an infusion over the first hour
  - 40 mg as an infusion over the following 2 hours

In patients with a bodyweight below 65 kg, the total dose should not exceed 1.5 mg/kg.

#### *Adjunctive Therapy*

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

### **Pulmonary Embolism**

A total dose of 100 mg should be administered in 2 hours. The recommended dose regimen is:

- 10 mg as an intravenous bolus over 1 - 2 minutes,
- 90 mg as an intravenous infusion over two 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 APPT values are less than twice the upper limit of normal. The infusion should be adjusted to maintain aPTT between 50 - 70 seconds (1.5 to 2.5 fold of the reference value).

### **Acute Ischaemic stroke**

The recommended dose is 0.9 mg/kg (maximum of 90 mg) infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus. Treatment should be initiated as early as possible 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.

#### **Notes:**

- a) For exact dosing, administration of ACTILYSE with an infusion pump is preferable, however, a gravity infusion set can be used instead.
- b) To give the patient the maximum benefit of ACTILYSE, residual volume remaining in i.v. application devices should be kept to a minimum.

### **Administration**

Under aseptic conditions the contents of an injection vial of ACTILYSE (10, 20 or 50 mg) dry substance is dissolved with sterilised water for injection according to the following table to obtain a final concentration of 1 mg alteplase per ml.

ACTILYSE vial	10 mg	20 mg	50 mg
Volume of sterilised water for injections to be added to dry substance	10 ml	20 ml	50 ml

Thus, for reconstitution to the final concentration of 1mg alteplase per ml the full volume of solvent provided should be transferred into the vial containing the ACTILYSE dry substance. For this purpose a transfer cannula is included with the pack-sizes of 20 mg and 50 mg. For the pack-size of 10 mg a syringe should be used. When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation.

Since the vial containing ACTILYSE has negative pressure, insert one end of the transfer set into the vial containing water for injection first. Only then, puncture the ACTILYSE vial with the other end of the transfer set. The reconstituted solution should then be administered intravenously as described above.

The reconstituted preparation is a clear and colourless to pale yellow solution. Prior to administration it should be inspected visually for particles and colour. It 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 dilution of the reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended.

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

## Contraindications

Generally, in all indications ACTILYSE should not be administered to patients with known hypersensitivity to the active substance alteplase, gentamycin (a trace residue from the manufacturing process) or to any of the excipients.

As with all thrombolytic agents, and generally, in all indications ACTILYSE should not be used in cases where there is a high risk of haemorrhage such as:-

- present significant bleeding disorder or within the past 6 months, known haemorrhagic diathesis
- any history central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- history or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage.
- prolonged or traumatic cardiopulmonary resuscitation (>2 minutes), obstetrical delivery within the past 10 days, recent puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein puncture)
- major surgery or significant trauma within 10 days, (this includes any trauma associated with the current acute myocardial infarction) recent trauma to head or cranium.
- severe uncontrolled arterial hypertension
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastrointestinal disease during the last 3 months
- arterial aneurysms, arterial / venous malformations
- neoplasm with increased bleeding risk

- severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- in patients receiving oral anticoagulants, e.g. warfarin sodium. (INR>1.3)
- hypersensitivity to the active substance alteplase or to any of the excipients

### **Additional Contraindications for patients with Acute Myocardial infarction or Pulmonary Embolism**

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 4.5 hours

### **Additional Contraindications for patients with Acute Ischaemic Stroke**

- symptoms of ischaemic attack 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 only minor before start of infusion
- severe stroke as assessed clinically (e.g. 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<sup>3</sup>
- systolic blood pressure > 185 or diastolic blood pressure > 110 mm Hg, or aggressive management (IV medication) necessary to reduce blood pressure to these limits
- blood glucose < 50 or > 400 mg/dl

ACTILYSE is not indicated for the therapy of acute stroke in children and adolescents under of 18 years. For use in patients above 80 years of age please refer to Warnings and Precautions.

## **Warnings and Precautions**

The appropriate presentation of alteplase product should be chosen carefully and in accordance with the intended use. The 2 mg presentation of alteplase is not indicated for use in acute myocardial infarction, acute pulmonary embolism or acute ischaemic stroke (due to risk of massive under dosing). Only the 10, 20 and 50 mg presentations are indicated for use in these indications.

ACTILYSE should only be used by physicians experienced in the use of thrombolytic treatment and with facilities to monitor that use. As with other thrombolytics, it is recommended that when ACTILYSE is administered standard resuscitation equipment and medication be available in all circumstances.

### **Bleeding**

The most common complication encountered during ACTILYSE therapy is bleeding. The concomitant use of heparin anticoagulation 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 possible bleeding sites (including those following catheter insertion, 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 ACTILYSE.

Should serious bleeding occur, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued and 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.

A dose exceeding 100 mg of ACTILYSE should not be given in acute myocardial infarction as well as pulmonary embolism and 90 mg in acute ischaemic stroke because it has been associated with an increase in intracranial bleeding.

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. Anaphylactoid reactions associated with the administration of ACTILYSE are rare and can be caused by hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. The stopper of the glass vial with ACTILYSE powder contains natural rubber (a derivative of latex) which may cause allergic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment should be initiated.

Monitoring is recommended particularly for patients receiving ACE-inhibitors concomitantly (see Adverse Effects). As with all thrombolytics, 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:

- Recent intramuscular injection or small recent traumas, such as biopsies, puncture of major vessels, cardiac massage for resuscitation.
- Conditions with an increased risk of haemorrhage, which are not mentioned under contraindications.

When ACTILYSE is being considered for the treatment of pulmonary embolism, 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 data regarding positive effects on mortality and late morbidity when a thrombolytic agent is used to treat pulmonary embolism.

**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:**

**Arrhythmias**

Coronary thrombolysis may result in arrhythmia associated with reperfusion. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

**Glyco-Protein 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 stroke the following special warnings and precautions apply in addition:**

Treatment must be performed only by a physician trained and experienced in neurological care.

Compared to 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 Contraindications and in general all situations involving a high risk of haemorrhage
- small asymptomatic aneurysms of the cerebral vessels
- late time-to-treatment onset
- patients pre-treated with acetyl salicylic 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.
- patients over 80 years of age may have an increased risk of intracerebral haemorrhage and a reduced net benefit from treatment compared to younger patients. Therefore, the use of ACTILYSE should be weighed carefully against anticipated risks on an individual patient basis.

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 with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dl or >400 mg/dl 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.

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

### **Pregnancy and Lactation**

There is very limited experience with the use of ACTILYSE during pregnancy and lactation. In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.

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

### **Effects on Ability to Drive and Use Machines**

Not applicable.

## **Adverse Effects**

### **Indications myocardial infarction, acute pulmonary embolism and acute ischaemic stroke:**

The most frequent adverse reaction associated with ACTILYSE is bleeding ( $>1:100$ ,  $\leq 1:10$ : major bleeds;  $>1:10$ : 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.

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

The classification of fat embolism, which was not observed in the clinical trial population, was based on spontaneous reporting.

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 of myocardial infarctions were presumably attributable to the small sample size. Except for intracranial haemorrhage a side effect in the indication stroke and reperfusion arrhythmias 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:

anaphylactoid reactions, which are usually mild, but can be life threatening in isolated cases. 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 Enzymes inhibitors. No definite anaphylactic (IgE mediated) reactions to ACTILYSE are known. Transient antibody formation to ACTILYSE has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

#### Eye disorders:

eye haemorrhage

#### Cardiac disorders:

pericardial haemorrhage

#### Vascular disorders:

haemorrhage (such as haematoma)

embolism, which may lead to corresponding consequences in the organs concerned  
bleeding of parenchymatous organs such as

- hepatic haemorrhage
- pulmonary haemorrhage

#### Respiratory, thoracic and mediastinal disorders:

respiratory tract haemorrhage such as

- pharyngeal haemorrhage
- haemoptysis
- epistaxis

Gastrointestinal disorders gastrointestinal haemorrhage such as

- gastric haemorrhage
- gastric ulcer haemorrhage
- rectal haemorrhage
- haematemesis
- melaena
- mouth haemorrhage
- gingival bleeding

retroperitoneal haemorrhage, such as retroperitoneal haematoma

nausea

vomiting

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

Skin and subcutaneous tissue disorders:

ecchymosis

Renal and urinary disorders:

urogenital haemorrhage such as

- haematuria
- haemorrhage urinary tract)

General disorders and administration site conditions:

injection site haemorrhage, puncture site haemorrhage such as

- catheter site haematoma
- catheter site haemorrhage)

Investigations:

blood pressure decreased

body temperature increased

Injury and poisoning and procedural complications:

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

Surgical and medical procedures:

transfusion

**Indication myocardial infarction:**

Cardiac disorders:

reperfusion arrhythmias, such as

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

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

### **Indications myocardial infarction and pulmonary embolism:**

Nervous system disorders

intracranial haemorrhage such as

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

### **Indication acute ischaemic stroke:**

Nervous system disorders:

intracranial haemorrhage such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation of 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.

### **Interactions**

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 (eg coumarin derivatives, platelet aggregation inhibitors, heparin) may increase the risk of bleeding prior to, during or after ACTILYSE therapy.

Concomitant treatment with ACE inhibitors may enhance the risk of suffering an anaphylactoid reaction, as in the cases describing such reactions a relatively larger proportion of patients were receiving ACE inhibitors concomitantly.

### **Overdosage**

Notwithstanding the relative fibrin specificity of ACTILYSE, a clinically significant 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.

### **Pharmaceutical Precautions**

Protect from light.

Store below 25°C

The reconstituted solution can be kept for up to 24 hours in a refrigerator and up to 8 hours at temperatures up to a maximum of 25°C. However, 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.

### **Medicine Classification**

Prescription Medicine

## **Package Quantities**

Individual packs of ACTILYSE 10mg injection vial and 10ml water for injection, ACTILYSE 20mg injection vial and 20ml water for injection (not marketed), and ACTILYSE 50mg injection vial and 50ml water for injection.

## **Further Information**

ACTILYSE<sup>®</sup> is a registered trademark.

## **Excipients**

L-arginine, phosphoric acid, polysorbate 80, gentamycin (a trace residue from the manufacturing process).

## **Incompatibilities**

The reconstituted solution may be diluted further with sterile physiological saline solution (0.9 %) up to a minimal concentration of 0.2 mg alteplase per ml since the occurrence of turbidity of the reconstituted solution can not be excluded.

Further dilution with sterilised water for injections or the use of carbohydrate solutions is not recommended due to increasing formation of turbidity of the reconstituted solution.

ACTILYSE should not be mixed with other drugs (not even heparin), in the same infusion vial nor the same intravenous line (see Dosage and Administration).

Source Document BPI No.: 0002-10 dated 20.10.2009

## **Name and Address**

Boehringer Ingelheim (N.Z.) Limited  
P O Box 76-216  
Manukau City  
Auckland  
NEW ZEALAND

Telephone: (09) 274 8664  
Facsimile: (09) 271 0629

## **Date of Preparation**

9 September 2011