1. NAME OF THE MEDICINAL PRODUCT

Actilyse® powder and solvent for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains: 50 mg alteplase

1 vial of solvent contains: 50 mL sterilised water for injections

excipients: l-arginine, phosphoric acid, polysorbate 80

The reconstituted solution contains 1 mg alteplase per mL.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Thrombolytic treatment in acute myocardial infarction

90 minutes (accelerated) dose regimen (see section Dosage and administration): for patients in whom treatment can be started within 6 hours of symptom onset;

3 hour dose regimen (see section Dosage and administration): for patients in whom treatment can be started between 6 - 12 hours after symptom onset.

ACTILYSE has proven to reduce 30-day-mortality in patients with acute myocardial infarction.

Thrombolytic treatment in 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 are no clinical trials on mortality and late morbidity related to pulmonary embolism.

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.

4.2 Posology and method of administration

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

Acute myocardial infarction

a) 90 minutes (accelerated) dose regimen

for patients with acute myocardial infarction, in whom treatment can be started within 6 hours after symptom onset.

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)

b) 3 hours dose regimen

for patients with acute myocardial infarction, in whom treatment can be started between 6 and 12 hours after symptom onset~~:~~.

In patients with a body weight ≥ 65 kg:

- 10 mg as an intravenous bolus, immediately followed by
- 50 mg as an intravenous infusion over the first hour, immediately followed by
- 40 mg as an intravenous infusion over two hours, until the maximum total dose of 100 mg

In patients with a body weight < 65 kg:

- 10 mg as an intravenous bolus, immediately followed by
- an intravenous infusion over three hours up to a maximum total dose of 1.5 mg/kg body weight

Adjunctive therapy:

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

<u>Acute massive pulmonary embolism</u>

In patients with a body weight ≥ 65 kg:

A total dose of 100 mg should be administered in 2 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 two 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 two hours up to a maximum total dose of 1.5 mg/kg body weight

Adjunctive therapy:

After treatment with ACTILYSE heparin therapy should be initiated (or resumed) when aPTT 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).

<u>Acute ischaemic stroke</u>

The recommended total dose is 0.9 mg/kg body weight (maximum of 90 mg) starting with 10% of the total dose 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 within 4.5 hours of symptom onset, see section Special warnings and precautions. 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* (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
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
* given in a concentration of 1 mg/ml over 60 min.			

Adjunctive therapy:

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 the symptom-onset 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.

Method of administration

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

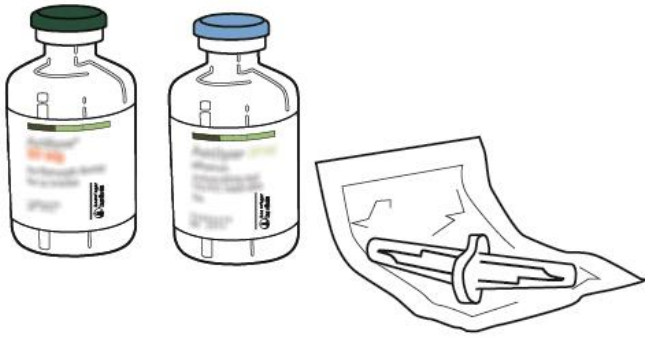
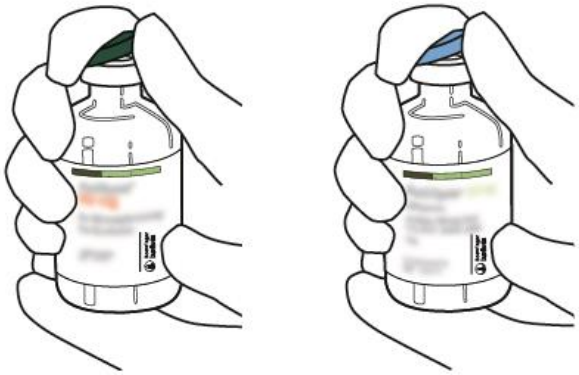
Instructions for use

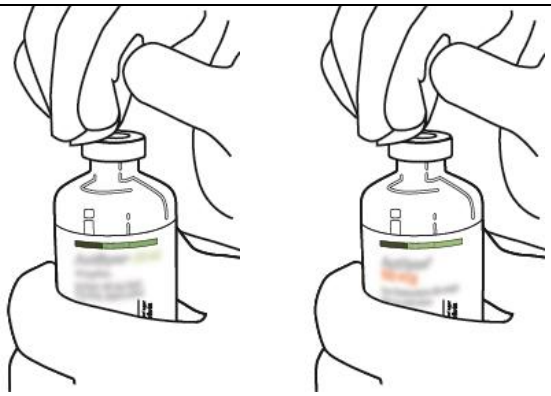
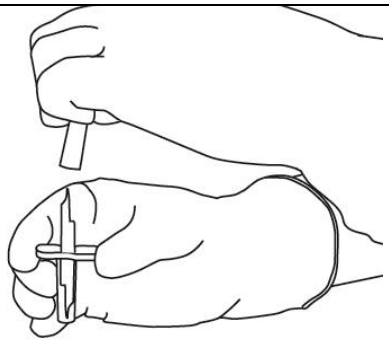
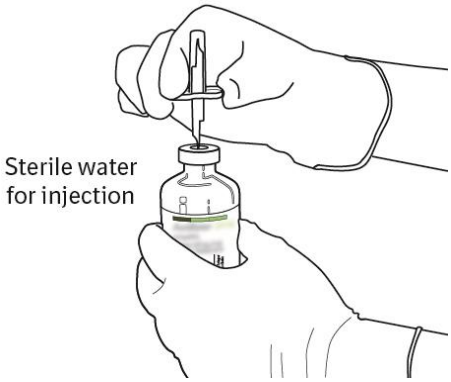
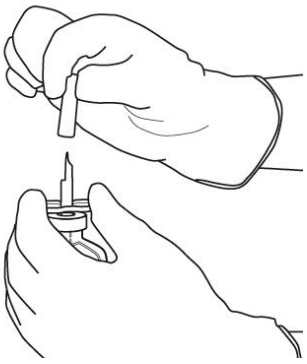
Under aseptic conditions the contents of an injection vial of ACTILYSE (50 mg) dry substance is dissolved with sterilised water for injection according to the following table to obtain a final concentration of 1 mg alteplase per mL.

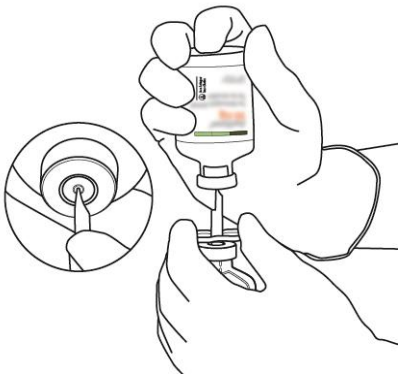
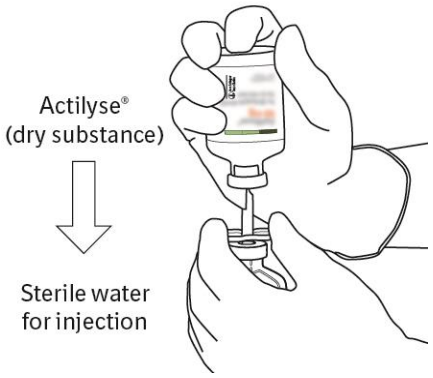
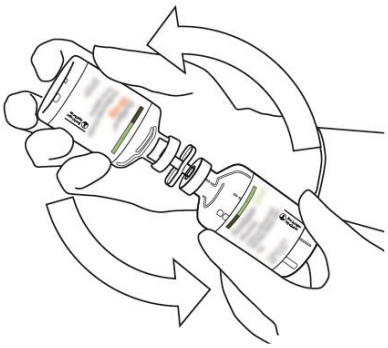
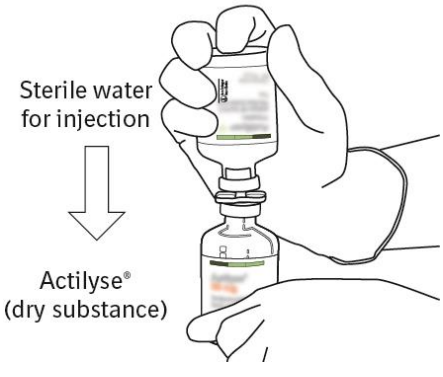
ACTILYSE dry substance	50 mg
Volume of sterilised water for injections to be added to dry substance	50 mL
Final concentration:	1 mg alteplase/mL

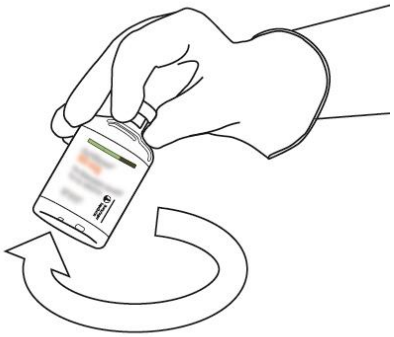
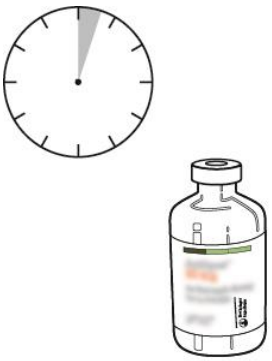
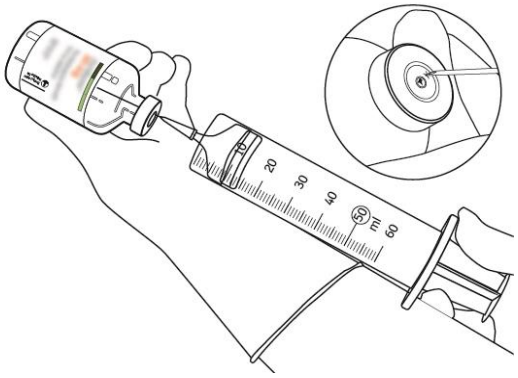
For this purpose a transfer cannula is included with the pack-sizes of 50 mg.

<u>Instructions for reconstituting Actilyse</u>

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 vertically 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 sustance.	 

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 reconstituted solution consists of 1 mg/mL Actilyse. It should be clear and colurless 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.	

(*if a transfer cannula is included in the kit. The reconstitution can also be performed with a syringe and a needle).

4.3 Contraindications

ACTILYSE is contraindicated in

- patients with known hypersensitivity to the active substance alteplase or to any of the excipients
- cases where there is a high risk of haemorrhage such as:
  - significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
  - patients receiving effective oral anticoagulant treatment, (e.g. warfarin sodium with INR > 1.3) (please see section Special warnings and precautions, subsection "Bleeding")
  - any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
  - history or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
  - severe uncontrolled arterial hypertension
  - major surgery or significant trauma in the past 10 days (this includes any trauma associated with the current acute myocardial infarction), recent trauma to head or cranium
  - 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)
  - severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
  - bacterial endocarditis, pericarditis
  - acute pancreatitis
  - documented ulcerative gastro-intestinal disease during the last 3 months
  - arterial aneurysms, arterial/venous malformations
  - neoplasm with increased bleeding risk

In the indications acute myocardial infarction the following contraindications apply in addition:

- 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

In the indications acute massive pulmonary embolism the following contraindications apply in addition:

- 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

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

- 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^3
- systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg, or aggressive management (IV medication) necessary to reduce blood pressure to these limits
- blood glucose < 50 mg/dL or > 400 mg/dL
- children under 16 years of age (for children ≥ 16 years of age see section Special warnings and precautions)

4.4 Special warnings and precautions for use

The following special warnings and precautions apply for the treatment of acute myocardial infarction, acute massive pulmonary embolism and acute ischaemic stroke:

ACTILYSE should be used by physicians experienced in the use of thrombolytic treatment and with the 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.

Hypersensitivity

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 Contraindications).

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.

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

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

Patients treated for any authorised indication should be monitored for angio-oedema during and for up to 24h 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.

Bleeding

The most common complication encountered during ACTILYSE therapy is bleeding. 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 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.

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
- 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 the following special warnings and precautions apply in addition:

- systolic blood pressure > 160 mmHg, see also section Contraindications
- advanced age, which may increase the risk of intracerebral haemorrhage. As the therapeutic benefit is also positive in elderly patients, the risk-benefit-evaluation should be carried out carefully.

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-ProteinIIb/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 massive pulmonary embolism the following special warnings and precautions apply in addition:

- systolic blood pressure > 160 mmHg, see also section Contraindications
- advanced age, which may increase the risk of intracerebral haemorrhage. As the therapeutic benefit is also positive in elderly patients, the risk-benefit-evaluation should be carried out carefully.

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

Treatment must be performed under the responsibility of physician trained and experienced in neurological care. For the verification of treatment indication remote diagnostic measures may be considered as appropriate (see section Indications; 3. Thrombolytic treatment of acute ischaemic stroke).

Bleeding

Intracerebral haemorrhages represent the major adverse event (up to approximately 15% of patients). However, this had not shown an increased overall morbidity or mortality.

Compared to 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 Contraindications and in general all situations involving a high risk of haemorrhage
- 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.
- Compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment and may have an increased risk of intracerebral haemorrhage when thrombolysed. 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. In general, the benefit-risk of thrombolysis in patients of advanced age remains positive. Thrombolysis in AIS patients should be evaluated on individual benefit-risk basis.

Treatment must 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 monitoring

Blood pressure (BP) monitoring during treatment administration and up to 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

The therapeutic benefit is reduced in patients who have had a prior stroke (see also section Contraindications) or in whom uncontrolled diabetes exists. The benefit/risk ratio is considered less favourable, 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.

In stroke patients the likelihood of a favourable outcome decreases with longer time to treatment from onset of symptoms, increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or symptomatic intracranial bleeding increases, independently of treatment.

Cerebral oedema

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

Paediatric population

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

In children ≥ 16 years of age the benefit should be weighed carefully against the risks on an individual basis.

Children ≥ 16 years of age should be treated according to the treatment guidance for the adult population after confirmation of thromboembolic arterial ischaemic stroke (ruling out "stroke mimics").

Traceability

In order to improve tracebility of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

4.5 Interaction with other medicinal products 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.

Drug 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 and should be avoided in the first 24 hours after treatment for acute ischaemic stroke, see section Contraindication.

ACE inhibitors

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of ACTILYSE in pregnant women.

Non-clinical studies performed with alteplase in doses higher than human doses exhibited fetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the drug. Alteplase is not considered to be teratogenic (see section 5.3 Preclinical safety data).

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

Lactation

It is not known if alteplase is excreted into human 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. Non-clinical studies performed with alteplase showed no adverse effect on fertility (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The most frequent adverse reaction associated with ACTILYSE is bleeding (≥ 1:100 to < 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 haemorrhage neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion may be associated.

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 side effect in the indication acute ischaemic stroke as well as for reperfusion arrhythmias 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:

- anaphylactoid reactions, which are usually mild, but can be life threatening in isolated cases.

They may appear as

- rash
- urticaria
- bronchospasm
- angioedema
- hypotension
- shock or any other symptom associated with hypersensitivity.

Nervous system disorders:

- intracranial haemorrhage such as

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

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

Respiratory, thoracic and mediastinal disorders:

- respiratory tract haemorrhage, such as

  - pharyngeal haemorrhage
  - haemoptysis
  - epistaxis
  - pulmonary haemorrhage

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

*Fat embolism was not observed in the clinical trial population, but was found in spontaneous reporting.

List of additional adverse reactions for the indication acute myocardial infarction:

Cardiac disorders:

- reperfusion arrhythmia, such as

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

4.9 Overdose

Symptoms

If the maximum recommended dose is exceeded the risk of intracranial bleeding increases.

The relative fibrin specificity notwithstanding, a clinically significant reduction in fibrinogen and other blood coagulation components may occur after overdose.

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

Pharmacotherapeutic group: Antithrombotic agents

ATC code: B01AD02

Mode of Action

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.

Pharmacodynamics

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.

Clinical Trials

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 intravenous 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 subcutaneous or intravenous heparin (7.3%). The 1% absolute decrease in 30-day mortality for ACTILYSE compared to streptokinase was statistically significant ($p = 0.001$).

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 (α-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.

Acute massive 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. Thrombolysis in AIS patients should be evaluated on individual benefit-risk 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 (SmPC) 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 any ICH/SICH was higher with alteplase versus placebo (any ICH 27.0% versus 17.6%, $p = 0.0012$; SICH by NINDS definition 7.9% versus 3.5%, $p = 0.006$; SICH by ECASS III definition 2.4% versus 0.2%, $p = 0.008$).

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 21,566 patients in the 0 to 3 hours time window were compared with data from 2,376 patients treated between 3 to 4.5 hours after onset of AIS (data from 2010). 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 (7.4%) as compared with the up to 3 hours time window (7.1% ; adjusted odds ratio 95% CI:1.18 (0.99-1.41 p=0.06)). Mortality rates at 3 months were similar for the 3 to 4.5 hours time window (12.0%) with the 0 to 3 hours time window 12.3%.

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 $T_{1/2}$ 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.

5.3 Preclinical safety data

In subchronic toxicity studies in rats and marmosets no other unexpected side effects than increased bleeding tendency at higher doses were found.

No indications of a mutagenic potential were found in mutagenic tests.

In pregnant animals no teratogenic effects were observed after intravenous infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryolethality, growth retardation) was induced by more than 3 mg/kg/day. No effects on peri-postnatal development or on fertility parameters were observed in rats with doses up to 10 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
L-arginine
Phosphoric acid
Polysorbate 80

Solvent:
Water for injections

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 injections 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 drugs, neither in the same infusion-vial nor the same venous line (not even with heparin).

6.3 Shelf life

Unopened vials

3 years

Reconstituted solutions

The reconstituted solution has been demonstrated to be stable for 24 hours at 2-8ºC and for 8 hours at 30ºC.

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

Protect the lyophilised substance from light.

Store below 30°C

6.5 Nature and contents of container

Pack with 1 vial containing 50 mg of the active ingredient and 1 vial with 50 mL water for injections.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Thai) Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

1C 260/31

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 22 September 1988
Date of latest renewal: 27 August 2024

10. DATE OF REVISION OF THE TEXT

27 August 2024